

NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME IV PANEL REPORTS

PART I

REPORT OF THE HEART AND BLOOD VESSEL DISEASES PANEL



APRIL 6, 1973

U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE

Public Health Service

National Institutes of Health

National Heart and Lung Institute

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APRIL 8, 1973

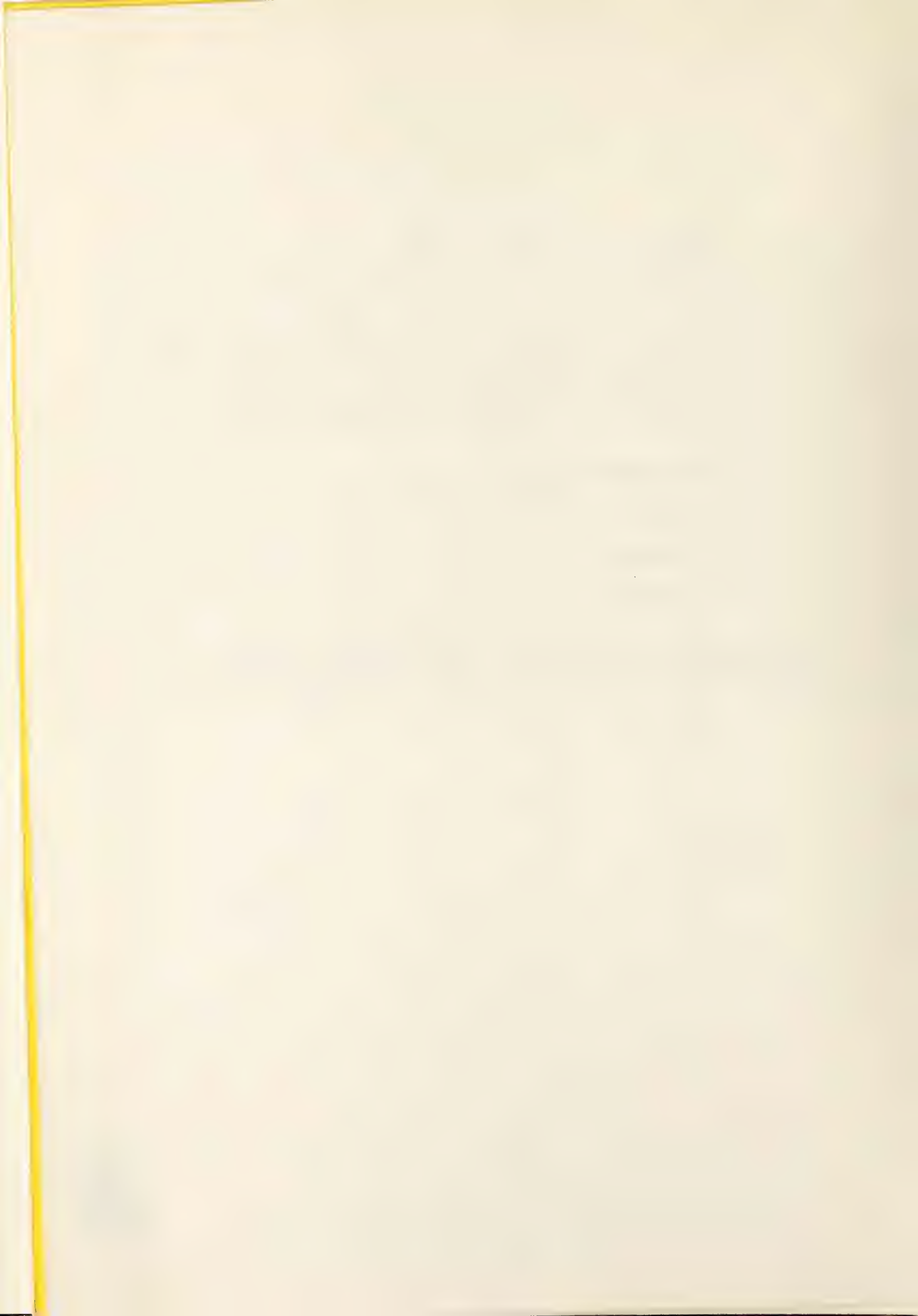
F O R E W O R D

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423) requires that the National Heart and Lung Institute develop a plan for a National Heart, Blood Vessel, Lung and Blood Disease Program. The Institute established a committee of four panels to assist in the development of program plans for each of the four major program areas:

- Heart and Blood Vessel Diseases
- Lung Diseases
- Blood Diseases
- Blood Resources.

This report was prepared by the Heart and Blood Vessel Diseases Panel.





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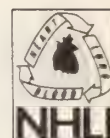
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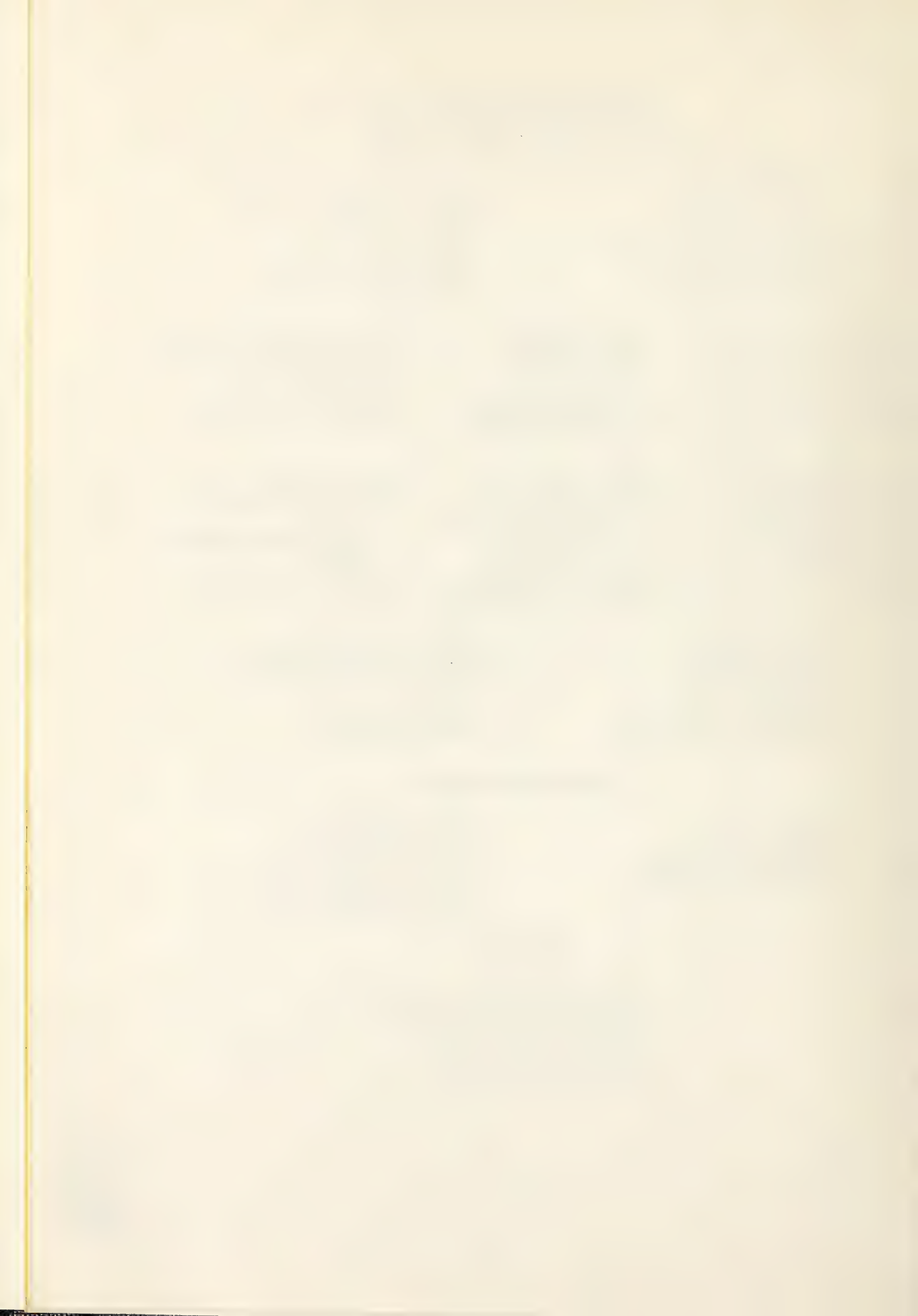


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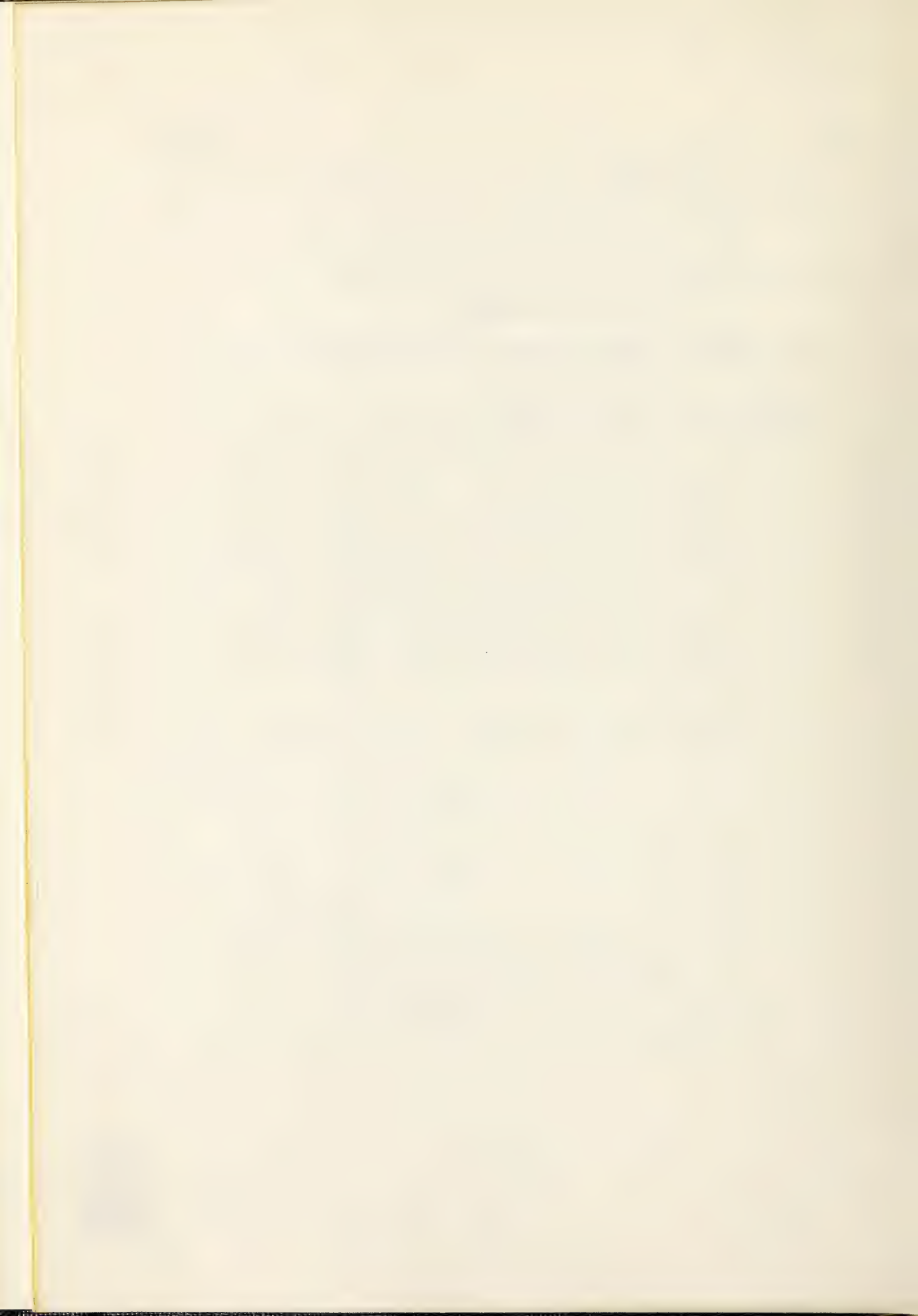
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P R E F A C E

The Ninety-Second Congress enacted the National Heart, Blood Vessel, Lung and Blood Act of 1972 (Public Law 92-423) to plan and target the attack on this major national problem. A Heart and Blood Vessel Diseases Panel, consisting of 10 physicians representing various interests and disciplines concerned with the problem of cardiovascular disease, was appointed to prepare this plan. Members of the Panel served as the chairpersons of the 11 Task Groups appointed to consider specific problem areas of cardiovascular disease. There were 92 members on the Heart and Blood Vessel Disease Task Groups; most were doctors of medicine, but basic scientific activities of the participants varied from laboratory basic science, to clinical investigation, to the practice of cardiovascular medicine or surgery. Sixty-four medical centers in 25 states were represented on the Heart and Blood Vessel Diseases Panel and on its 11 Task Groups. (See Appendix A).

Data from the several Task Group meetings were collated as scientific summaries, the basic information components from which this report was constructed. The fundamental structural unit was an approach to a particular problem; each approach was supplemented by component project area descriptions which outlined the steps to be employed to attain a specific objective. Consultants often collaborated with Task Group members to prepare the approach and project area descriptions for their particular field of expertise. All



scientific summaries were reviewed by the other members of the Task Group, and corrections and additions were incorporated into subsequent drafts. Each Task Group chairman then synthesized the approach descriptions into a narrative summary. A list of recommendations was prepared and agreed upon by each Task Group and accompanied the narrative summary. Suggestions for modifications of these documents were solicited from each Task Group member and incorporated into the revised summary; therefore, the narrative summaries and recommendations for each problem area represent a synthesis of the Task Group effort and a consensus of the Task Group members. The current volume represents a condensation of material originally contained on more than 2000 pages of scientific summary sheets and corresponding narratives.

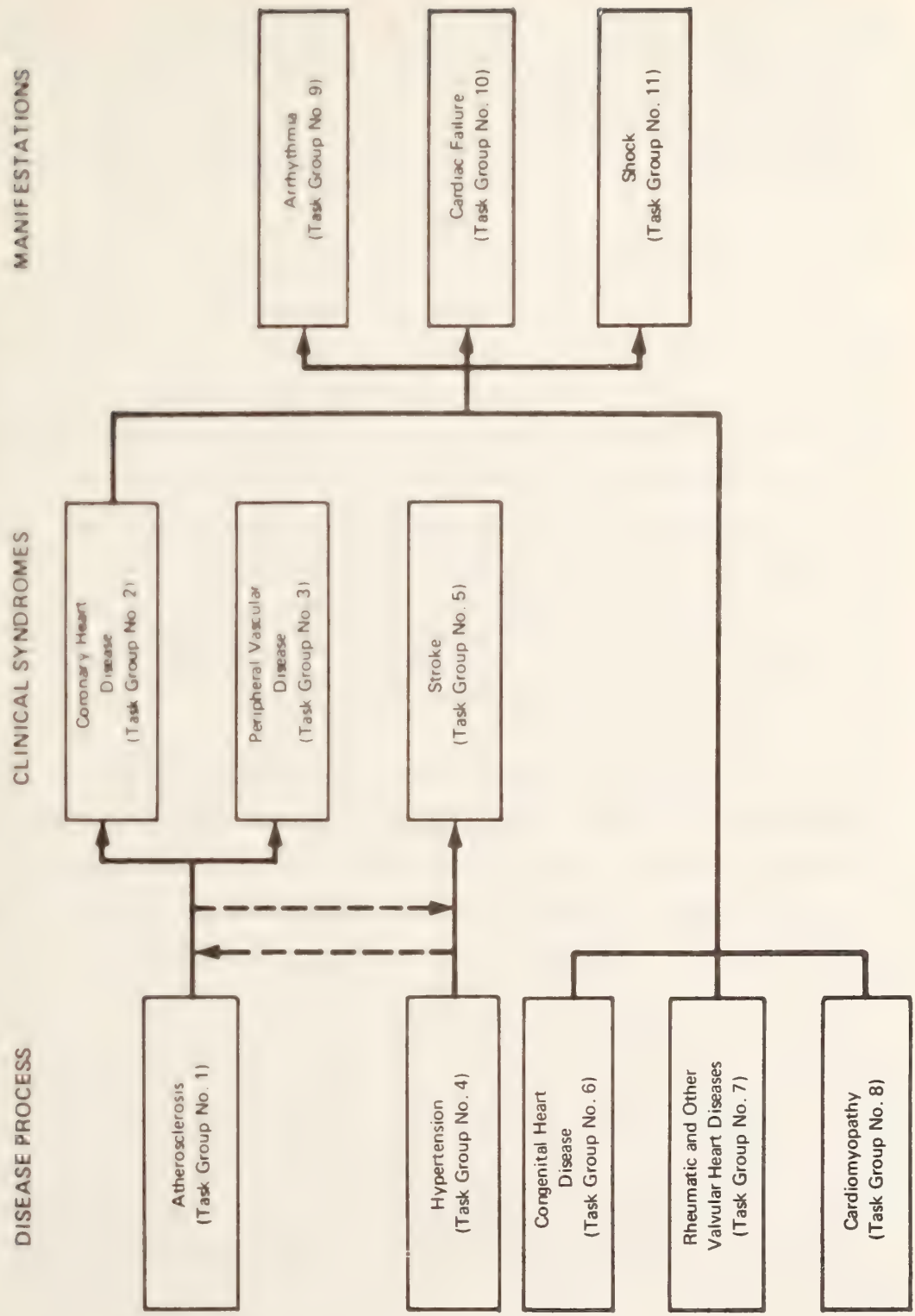
The Task Group narrative summaries prepared by the Task Groups were edited and condensed by the Panel chairman and co-chairman for inclusion here in the Panel report. Each Panel member had the opportunity to review and modify the edited version of his Task Group narrative summary which appears in final form in Part II.

The Panel report is subdivided into five major parts. Part I provides historical background and perspective. Part II, entitled "The Problems and Proposed Programs," consists of 11 sections which follow the Task Group organization of the Panel, and which are based on accepted concepts of the pathogenesis of heart disease. A simplified model of this process is shown schematically in Figure 1. Atherosclerosis is the major disease process responsible for coronary heart disease and peripheral vascular disease and is also important in stroke; the first Task Group (2.1) deals with this process.



Figure 1

HEART DISEASES - RELATIONSHIPS WITH TASK GROUPS



The sections which follow deal with the major clinical consequences of atherosclerosis: coronary heart disease (2.2) and peripheral vascular disease (2.3). Task Group Four was concerned with hypertension (2.4), the other major disease process which, along with atherosclerosis, underlies most cases of stroke, the subject of the next section (2.5). Therefore, the first five Task Groups cover two major disease processes: atherosclerosis and hypertension, and the major clinical syndromes which they produce: coronary heart disease, peripheral vascular disease and stroke. Each of the next three sections deals with another disease process and its manifestations: congenital heart disease (2.6), rheumatic and other valvular heart diseases (2.7) and cardiomyopathy (2.8). The final three sections deal with the manifestations of disease or the syndromes which may result from heart disease of any type: arrhythmia (2.9), cardiac failure (2.10) and shock (2.11).

Part III summarizes Task Group recommendations in four major categories: first, the acquisition of new knowledge through research; second, the development of new techniques; third, the evaluation of existing therapy; and lastly, the immediate application of existing knowledge. Part IV, entitled "The Legislation and the Proposed Program," organizes the Panel report in accordance with the 10 legislative requirements. Each of the 10 elements was correlated by a Panel member from review of the Task Group narrative summaries and recommendations. Part V lists all of the Task Group recommendations for reference purposes; these recommendations are identical to those at the end of each Task Group section in Part II.



The Appendices contain the lists of Task Group members (Appendix A) and graphs of the number distribution of project areas with respect to the legislative requirements and program objectives (Appendix B). Appendix C is a listing of the problems, approaches and project areas considered.



PART I

INTRODUCTION



PART I
INTRODUCTION

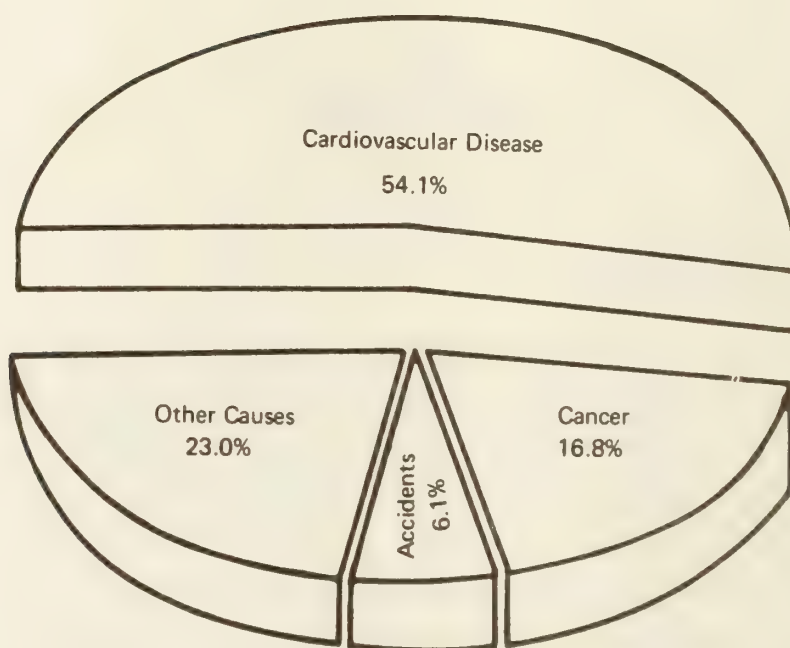
1.1 BACKGROUND

Heart disease has been the major cause of death in the United States since the 1920's. Although there has been a decline in death and disability attributable to rheumatic fever, hypertension and stroke, heart disease still accounts for 54 percent of all deaths¹ in this country (Figure 1-1). The death rate from heart disease is 365 per 100,000 of population annually. This rate is more than twice the death rate from cancer, the next highest cause of death in the United States. It has been estimated that if heart disease deaths could be eliminated, life expectancy would increase by approximately 11 years. Each year one million

¹National Center for Health Statistics: Vital Statistics of the United States, 1967; Volume II – Mortality, Part A, HEW, Public Health Service, 1969



Figure 1-1
DEATHS FROM ALL CAUSES, UNITED STATES, 1967



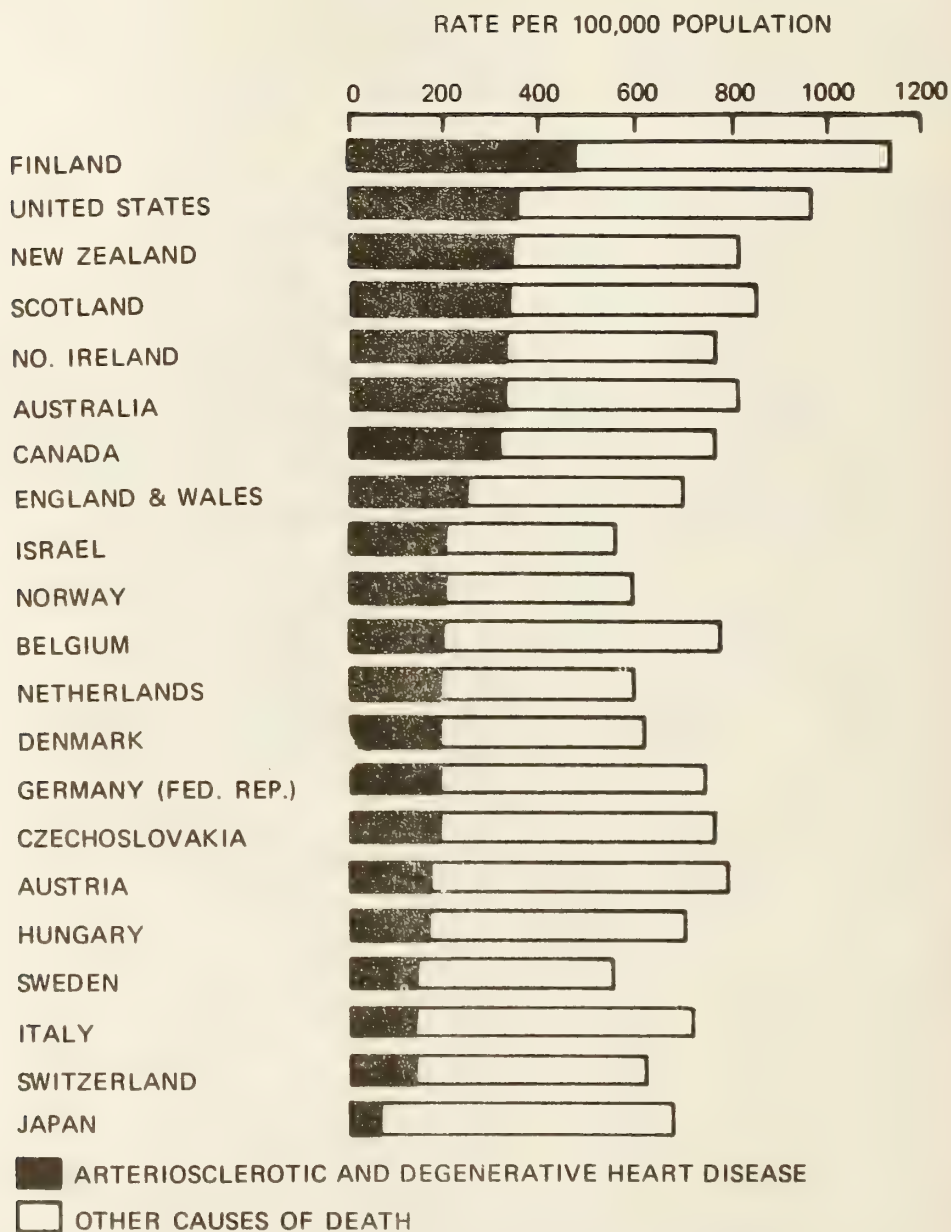
Americans die of heart disease and 250,000 succumb before the age of 65. The further tragedy of heart disease is reflected in this loss of life during years of peak productivity and responsibility. The annual cost of heart disease disability and death in the United States is estimated at more than \$30 billion.

International statistics² (Figure 1-2) indicate that the United States is second only to Finland in death rate from arteriosclerotic heart disease in men age 45 to 54. The death rate in Sweden, a country similar in many respects to Finland and the U.S., is far lower, being less than half that of the United States. These statistics indicate that a high death rate from arteriosclerotic coronary heart disease is neither inevitable nor necessary.

² World Health Organization: World Health Statistics Annual, 1967: Volume I, Vital Statistics and Causes of Death, 1970; Geneva, WHO, 1970



Figure 1-2
DEATH RATES FROM ARTERIOSCLEROTIC AND DEGENERATIVE
HEART DISEASE AND FROM ALL OTHER CAUSES*



*Selected Countries, 1967—Men Aged 45-54 Years

The establishment of the National Heart Institute in 1948 recognized the importance of cardiovascular disease to the health of the American people. The availability of new funding and resources provided tremendous impetus to heart disease research. The important discoveries, progress and accomplishments of the past 25 years have had a major impact on the health of the American people.

1. Approximately half of all in-hospital deaths from myocardial infarction were caused by sudden cardiac arrhythmias. Deaths from this cause have been virtually eliminated in hospitalized patients through the use of continuous electrocardiographic monitoring techniques and the development and application of new drugs and resuscitative techniques and equipment, closed chest cardiac massage, and defibrillators.
2. Hypertension is a major cause of heart failure and stroke and it is now possible to reduce significantly the incidence of stroke and heart failure by effective treatment of hypertension. This effective long-term treatment of hypertension has been made possible by the development of newer, more potent and better tolerated drugs.
3. The incidence of acute rheumatic fever and of subsequent chronic rheumatic heart disease has been reduced substantially by the prompt identification and treatment of streptococcal infection.
4. Great advances in vascular surgery now permit the replacement of diseased or occluded vessels with consequent improvement in the function of previously ischemic limbs, and the prevention of fatal rupture from aortic aneurysms.
5. The correction of the majority of congenital cardiac defects was made possible by the development of artificial heart-lung machines; many children born with heart defects have been restored to a normal productive life. These same devices have made possible the replacement of intracardiac valves and the grafting of vessels to replace diseased coronary arteries.



6. Intracardiac prostheses have been developed to replace diseased cardiac valves in many forms of valvular heart disease.
7. Disability and premature death from heart block can be prevented by the implantation of an electrical cardiac pacemaker.
8. Certain drugs (e.g., Thalidomide) and viral infections (e.g., German measles) are now recognized as causes of congenital heart disease. The appropriate testing of drugs, the avoidance of certain drugs during pregnancy, and antiviral immunization programs may have a significant impact on the incidence of congenital heart disease.
9. Improvements in the understanding and treatment of hemorrhagic and septic shock have served to reduce substantially the mortality from this serious complication.
10. The availability of new diuretic agents has improved the treatment of heart failure so that the productive life of afflicted individuals may be extended.
11. The inevitable early death of individuals with renal failure can now be prevented by hemodialysis and kidney transplantation.

The widespread implementation of new knowledge has permitted a substantial reduction in heart disease morbidity and mortality. No citizen must be denied the benefits of the knowledge we have acquired. However, our success to date has been largely in the realm of treatment of diseases after they are already manifest, rather than in the elucidation of the mechanisms involved in the development of the disease. Only by understanding of the factors involved in the development of the disease can we hope to prevent or arrest heart and blood vessel diseases.

The accomplishments of the last quarter century serve to highlight future needs. For example, fatal arrhythmias have been



essentially eliminated in patients with myocardial infarction in the coronary care unit. Yet we recognize that more than half of fatal arrhythmias occur in the first hour subsequent to myocardial infarction, long before most of these patients have even reached the hospital. There is much we can do with present knowledge to correct this problem. We can educate the public to recognize the symptoms of myocardial infarction and come to the hospital sooner. We can provide better emergency transportation. We can devise drugs for prophylactic administration to highly susceptible patients. However, all of these measures will be treating coronary occlusion after it has occurred and hence in an advanced stage of the disease. It would be preferable to prevent the occlusion of the coronary artery rather than to worry about its consequences. An analogy may be drawn from the field of infectious diseases. The development and utilization of the iron lung in the 1930's substantially reduced mortality from poliomyelitis by preventing death due to respiratory paralysis. This treatment, however, was directed at a manifestation of poliomyelitis. It was not until the development of the Salk and Sabin vaccines that the incidence of poliomyelitis fell from 57,879 cases in 1952 to 41 cases in 1967. Thereafter, the need for treating respiratory paralysis from poliomyelitis disappeared. We would not be concerned with arrhythmic death, heart failure or shock secondary to coronary artery occlusion and myocardial infarction if atherosclerosis of the coronary arteries could be prevented.

Another important example concerns patients with hypertension, most of whom can now be treated effectively with drugs; their useful productive lives can be prolonged by preventing or retarding the occurrence of stroke, heart attack, or heart



failure. Unfortunately, treatment requires lifelong adherence to a program of medication which must be supervised closely by skilled personnel. The available drugs still are imperfect and have many side effects. A high degree of patient motivation is needed to adhere to the treatment program, since most patients with hypertension have no symptoms until stroke, heart failure, or heart attack occurs. In most attempts at large-scale programs, treatment fails because of lack of patient acceptance of a concept of lifelong therapy. It would be preferable if the hypertension could either be prevented or cured. Certain forms of hypertension, such as that associated with narrowing of the renal arteries, may be cured by surgical correction of the partial obstruction. Several other relatively unusual forms of hypertension are also potentially curable. However, in a vast majority of hypertensive patients, the disease is not amenable to surgery. It is hoped that hypertension may one day be dealt with effectively in a similar fashion in this large group of patients for whom the cause and cure is not known.

The new knowledge required as a basis for the prevention, treatment and rehabilitation of patients with the major cardiovascular diseases is discussed in subsequent sections.

PART II

THE PROBLEMS AND PROPOSED PROGRAM



PART II
THE PROBLEMS AND PROPOSED PROGRAM

This section presents the program plan components developed by each of the 11 Task Groups of the Heart and Blood Vessel Diseases Panel. In each report, the problem is delineated, and the major approaches to and recommendations for achieving reductions in morbidity and mortality are presented.

2.1 ATHEROSCLEROSIS

2.1.1 Nature of the Disease and Scope of the Problem

Atherosclerosis is the major form of arteriosclerosis affecting the aorta and the arteries of the heart, brain, and legs. It is the principal cause of coronary heart disease, peripheral vascular disease, and aortic aneurysm; it is a major contributing cause of stroke and a cause of some types of kidney disease. It accounts for 84 percent of all cardiovascular deaths, representing approximately 840,000 persons.



Atherosclerosis begins early in life and progresses through adolescence and young adulthood into middle and older ages. It damages tissue by lessening the flow of blood through affected arteries and finally stopping the flow of blood completely. The individual is not aware of this process until it is far advanced and a vital organ is affected. Clinical manifestations begin after age 30 and become more frequent with increasing age. The sequelae of atherosclerosis comprise the major disease problems of the U.S. population, particularly of men, after 40 years of age.

2.1.2 What We Know About Atherosclerosis

Research efforts of the past 25 years have demonstrated that atherosclerosis and its clinical manifestations occur more frequently in persons with elevated blood lipids, persons with elevated blood pressure, persons who smoke cigarettes, persons who have a family history of atherosclerotic disease, and those with diabetes mellitus. Individuals who are physically inactive and those with certain personality types may also have a high risk of disease. These characteristics are known as "risk factors" and, although the mechanisms by which they influence atherosclerosis are not known, much indirect evidence provides hope that their modification will retard the progression of atherosclerosis and thereby prevent clinical disease. The evidence is best for cigarette smoking and indicates that the cessation of smoking is associated with a reduction in risk.

Research has also shown that the high prevalence and severity of atherosclerosis in countries such as the United States are associated with a high dietary intake of cholesterol and



saturated fats and with heavy cigarette smoking. Animal experiments and human studies have generally confirmed the importance of dietary cholesterol and saturated fat. These data provide strong hope that atherosclerosis may be prevented by modification of environmental factors, particularly diet and smoking.

Genetic characteristics that make certain individuals extremely susceptible to atherosclerosis have been identified, and specific biochemical markers for the characteristics are being sought. Precise identification of the highly susceptible person early in life offers a promising means of preventing premature atherosclerosis by modifying congenital risks through feasible techniques of hygiene and preventive medicine.

Much current research is directed at determining the mechanisms by which environmental factors, genetic traits, and risk factors interact to accelerate atherosclerosis and cause clinical disease. Techniques of biochemistry, physics, pathology, genetics, epidemiology, behavioral science, and many other disciplines have provided much information about etiology and pathogenesis. This rich background of basic knowledge has made possible many of the approaches that are being proposed for preventive regimens.

A promising beginning has been made in developing drugs and diets that lower serum lipid levels. Specifically, knowledge of cholesterol metabolism has led to the use of several drugs that lower serum lipid levels. Knowledge of the mechanisms of control and transport of blood lipids will lead to more effective drug therapy. The development of foods low in

cholesterol and saturated fat has been demonstrated to be technologically feasible, only an economic incentive is required to make such foods more readily available.

2.1.3 What We Need to Know About Atherosclerosis

The principal gap in our knowledge about atherosclerosis is the lack of certainty as to whether modification of exposure to environmental conditions and modification of risk factors will retard the progression of atherosclerotic lesions and prevent the occurrence of clinical disease in the general population, as contrasted with the high-risk population. Evidence bearing on this hypothesis is largely circumstantial and the rationale is largely one of analogy. We must test rigorously the feasibility of prevention of atherosclerosis in the general population through alteration of environmental conditions. The design of these tests should permit assessment of specific environmental agents, the most important of which is diet. Until this relatively direct scientific question is resolved through controlled clinical trials, progress toward long-range prevention is likely to be slow.

While existing knowledge is being tested through trial and application, continued expansion and enrichment of the fundamental knowledge about etiology and pathogenesis, particularly in selected areas described below, is the only source of ideas and hypotheses for more effective methods of prevention. As these are developed they must be tested in clinical trials.



2.1.4 Detailed Analysis of the Problem of Atherosclerosis

Eight major problems were selected as a structure for developing specific approaches to the overall problem of atherosclerosis. Each problem represents an interaction of genetic traits and environmental agents. Each problem requires a different combination of research, development, application, and education.

Hyperlipidemia

Hyperlipidemia, an abnormally high concentration of cholesterol, triglycerides, or both, in the blood is the strongest risk factor yet identified, has been the one most extensively investigated, and is amenable to modification in order to prevent or retard atherosclerosis. Diet is the principal environmental agent affecting serum lipid levels, and drugs are available that lower these blood levels. Several major forms of hyperlipidemia are genetically determined, and current research progress indicates that the mechanisms of their expression may be elucidated in the near future. Circumstantial evidence indicates that maintenance of low serum lipid concentrations from youth will retard the progression of atherosclerosis. Circumstantial evidence also indicated that reduction of hyperlipidemia in adulthood may cause regression of atherosclerosis lesions. The effects of lowering serum lipids on atherosclerosis in the general population should be tested in a conclusive manner.



Behavior

Behavior includes such components of life style as psychosocial stress, physical activity, traits that induce individuals to smoke cigarettes, and other conditions. Genetic constitution probably influences the behavioral reaction of the individual to his environment, but these genetic determinants are poorly defined. Intensified efforts are needed to define better the behavioral characteristics that predispose to atherosclerosis. In addition, it is important to find methods of motivating individuals to modify their behavior so that risk factors within their control are reduced. Operant conditioning has been suggested as a feasible approach to the modification of behavior.

Tissue Pathogenesis

Fundamental to an effective long-range program of preventing atherosclerosis is knowledge of how the lesions of atherosclerosis in the arterial wall begin and how they progress to occlude the artery, and knowledge of conditions or agents that influence progression. A better understanding of structure, biochemical composition, cellular physiology, and natural history of atherosclerosis in humans and experimental animals will provide a rational basis for improved methods of treatment and prevention.

Smoking

Cigarette smoking is a major risk factor for the diseases resulting from atherosclerosis, and is associated with more severe atherosclerosis. Evidence suggests that reduction in

smoking results in reduced morbidity and mortality. With such evidence, the inability of those concerned with health maintenance to alter the smoking behavior of the public is frustrating and mystifying. Continued and renewed efforts should be directed to reduce cigarette smoking and especially to prevent acquisition of the habit by young people. In view of the probability that much cigarette smoking will continue despite such efforts, we should seek to discover the way in which it affects atherosclerosis and how to circumvent this.

Blood Pressure

Elevated blood pressure confers increased risk of clinical disease and accelerates atherosclerosis. Although there is strong evidence that reduction in blood pressure by pharmacologic treatment reduces the incidence of stroke, we do not yet know whether or not such treatment reduces the incidence of other clinical sequelae of atherosclerosis. Therefore, the effectiveness of blood pressure reduction in retarding atherosclerosis should be tested and the mechanism by which hypertension produces its effects on atherosclerosis should be sought. (See 2.4, Hypertension)

Diabetes Mellitus

Diabetes mellitus (or impaired glucose tolerance) has long been recognized as associated with a higher frequency of atherosclerotic disease. If we could discover the mechanism by which diabetes produces its effect, we could devise methods of managing diabetes that would prevent the acceleration of atherosclerosis in patients with the disease.



Thrombosis

Although the clotting mechanism is clearly involved in the end stages of coronary heart disease, stroke, and peripheral vascular disease, we need to better define its role in the genesis and progression of the early lesions. (See Blood Diseases Panel Report)

Other Agents Associated with Atherosclerosis

Other suspected causative agents must not be neglected. They include the mineral content of drinking water, hyperuricemia, carbohydrate content of the diet, and arteritis.

2.1.5 Recommendations

Existing knowledge of the natural history of atherosclerosis indicates that prevention of arterial occlusion would prevent or retard most of the serious consequences in the target organs. Prevention of atherosclerosis should be the primary long-range strategy for reducing morbidity and mortality from coronary heart disease and peripheral vascular disease, and part of the strategy for reducing the incidence of stroke. In order to carry out this strategy the following specific programs are recommended as having the highest priority.

1. Define more completely the pathogenesis of atherosclerosis in terms of cellular biology, the chemistry of macromolecules, interactions of the arterial wall and elements of the circulating blood, the role of the hemostatic mechanism, and conditions that influence progression and regression of lesions.

2. Conduct controlled clinical trials to determine the effectiveness of specific risk factor reduction and environmental modification in retarding the progression of atherosclerosis and preventing clinical atherosclerotic disease. These specific trials should include the following:
 - Diet modification in closed and free-living populations
 - Serum lipid reduction by whatever methods are available--diet, drugs, surgery, or other methods that may be devised--to test the "lipid hypothesis"
 - Other specific risk factor modification, particularly hypertension.
3. Determine the mechanisms of biochemical genetic and behavioral control of blood lipids. Present research results are approaching the explanation of how lipoproteins are secreted into and removed from the plasma. There are many promising new fields of investigation including that of the role of behavioral factors in controlling blood lipids. Knowledge obtained through such research can lead to specific, rational methods for controlling hyperlipidemia.
4. Identify missing risk factors and etiologic agents. New prospective and experimental studies are needed to test specific hypotheses regarding yet unproven risk factors such as derangements of the hemostatic mechanism and behavioral traits. Genetic analyses should aid in identifying new risk factors and specific biochemical markers should be sought. Intensive study of risk factors in children is needed to identify persons at high risk as early in life as possible.
5. Identify individuals at high risk (hyperlipidemia, hypertension, smoking), and, through professional and public education, screening, referral, and follow-up, attempt to prevent atherosclerotic disease by "multifactor intervention." Give special attention to the adolescent, since the potential for prevention is greatest in the young.



6. Devise effective behavioral intervention methods to modify smoking, diet, adherence to medication, and other behavioral patterns identified as affecting risk of atherosclerosis.
7. Develop better hypolipidemic regimens such as drugs, foods, altered habits, surgical procedures, or other means of intervention that will lower serum lipids. Knowledge of the biochemical control of serum lipids and lipoproteins will contribute to such development. Foods low in cholesterol and saturated fat should be made available for high-risk persons and for clinical trials.
8. Intensify efforts to reduce cigarette smoking and particularly to prevent acquisition of the habit by the young.

2.2 CORONARY HEART DISEASE

2.2.1 Scope

Coronary heart disease or ischemic heart disease accounted for about 370,000 deaths in the United States in 1969. It is the largest single cause of death from cardiovascular disease and represents over one-third of the total. Coronary heart disease becomes the leading cause of death above age 30 in men. The disease affects men more commonly than women and, in 1969, 233,000 of the 370,000 deaths were men, 94,416 of whom were under the age of 65. Thus, approximately 100,000 men in the productive years of their life die of ischemic heart disease each year.

2.2.2 Challenge

The Coronary Heart Disease Task Group saw as its major challenge the patient with clinically evident coronary heart disease as distinguished from patients who have coronary atherosclerosis which has not as yet interfered with the function of the heart. The preferred long-range approach to this problem is the prevention of coronary atherosclerosis, which would indeed prevent coronary heart disease. However, even if a 100 percent effective program for the prevention of coronary atherosclerosis could be adopted immediately, coronary heart disease would continue to be a significant health problem for 20 to 30 years. This prediction is based on the observation that many young persons already have coronary artery lesions which may lead to symptomatic coronary artery disease in middle age or later. Preventive measures activated today probably would not alter these lesions significantly. Therefore,

any plan for the remainder of the twentieth century must include a large component directed at symptomatic coronary heart disease.

2.2.3 Balanced Approach

Fifteen approaches to the problem of coronary heart disease were defined which fell into four general categories. Several approaches represented the acquisition of fundamental knowledge upon which useful clinical information would be developed in the future. Other approaches were required to facilitate the application of existing knowledge. A third group included trials of existing forms of therapy and the fourth involved the immediate application of currently available methods of prevention and management. While the urgency of the coronary heart disease problem is recognized, the Task Group advises a balanced approach encompassing all appropriate approaches in all four categories outlined above since the application of existing knowledge alone is inadequate to control coronary heart disease.

2.2.4 Pathogenesis

There are many unanswered questions about the basic pathogenesis of coronary heart disease which are fundamental to the long-term solution to the problem. While atherosclerosis of the coronary arteries is clearly recognized as the underlying abnormality, the precipitating factors which, when superimposed on the underlying arterial lesions result in myocardial infarction, angina pectoris and death are poorly understood. The factors responsible for the transformation of the patient from asymptomatic coronary atherosclerosis to

symptomatic coronary heart disease is the major target for investigation. Only by obtaining a better understanding of responsible factors will it be possible to prevent this unfavorable evolution. A key focus is the interface between the blood vessel wall and the blood. The process or processes which bring about occlusion of the atherosclerotic coronary artery and subsequent myocardial infarction require further study before they can be effectively prevented or counter-acted.

2.2.5 Animal Models

There is no adequate animal model for human coronary heart disease. Consequently, much of the indicated investigation must be carried out in man until such time as an adequate animal model becomes available. The importance of a good animal model for clinical coronary heart disease exhibiting myocardial infarction, arrhythmia and sudden death was repeatedly emphasized. If such were available, studies of blood flow, collateral circulation development, drug action and the effects of surgical revascularization could be subjected to critical evaluation prior to their application in man. The development of such an animal model can accelerate progress in many areas and must, therefore, be given a high priority.

2.2.6 Clinical Investigation

The fundamental information which is required as a basis for any preventive or therapeutic approach can be acquired from clinical investigation of patients or from studies in adequate animal models. The prime targets would be the elucidation

of the factors responsible for the precipitation of coronary occlusion. Multidisciplinary studies are needed of the interface between the flowing blood and the vessel wall. The collateral circulation plays a key role in determining the extent and severity of myocardial damage from coronary occlusion but little is known about the factors controlling the development of these important vessels. The regulation of blood flow in the large coronary vessels and the distribution of blood flow within the myocardium need further study. Closely related are studies of drug action on blood flow particularly in relation to changes in the distribution of flow. The acquisition of fundamental new knowledge in all of these areas would certainly lead to clinical applications in the form of preventive and therapeutic measures.

2.2.7 Precipitating Factors

Knowledge of the factors that precipitate coronary heart disease are fundamental to the prevention of sudden death; 60 to 75 percent of patients who die from coronary heart disease do so before they reach the hospital, and 45 percent of coronary deaths occur within the first hour after the onset of symptoms. Improved methods of treating myocardial infarction are not likely to help many of these sudden death victims. Methods to detect the pre-infarction state and to prevent the occurrence of the terminal occlusive episode are needed. Early detection of advanced coronary atherosclerosis by non-invasive methods would assist in achieving this objective.



2.2.8 Classification of Coronary Heart Disease

Another area of importance is the need for a standardized system of classification of the various coronary heart disease syndromes. The time is right to utilize information derived from the clinical presentation, electrocardiography, coronary arteriography, echocardiography, and studies of left ventricular function to categorize patients more precisely. Emphasis is placed upon the importance of non-invasive methods, such as by ultrasonic methods, exercise electrocardiography and isotope techniques to supplement clinical descriptions. These noninvasive techniques should be standardized against currently established methods of evaluation, such as coronary arteriography. The noninvasive techniques could be incorporated into long-range epidemiological studies such as those being undertaken in lipid research centers in the hope that cases of inapparent heart disease could be detected at an early stage and the development of overt disease prevented.

2.2.9 Quantification of Disease

If a simple, safe, rapid test were available whereby the severity and extent of coronary atherosclerosis could be quantified in large numbers of patients at high risk, the risk of sudden death, myocardial infarction, or angina pectoris could be assessed prior to the advent of these clinical states. If it were possible to get the information now obtainable only from coronary arteriography by a simple non-invasive means, a great step forward would be possible.

2.2.10 Early Warning Symptoms

Public education concerning the early symptoms of coronary disease is needed. The importance of this approach depends upon the demonstration that ready availability of facilities for diagnosis and treatment of patients with chest pain would make a significant impact on the death rate. If this could be demonstrated, an all-out effort would be justified to educate the public as to the significance of chest pain and the steps which should be taken when it occurred. It was suggested that a group of science writers with a record of achievement in heart disease should be asked to form a nucleus about which the efforts of the advertising media and communications industry could be marshalled.

2.2.11 Evaluation of Medical and Surgical Therapy

All approaches to the therapy of angina pectoris and myocardial infarction depend upon the development of better methods of the quantification of coronary arterial disease, myocardial ischemia and infarction, and also upon the development of a standard system of classification and categorization which would make it possible to pool results obtained from a number of centers. With this system for the determination of input and end points, it would be possible to evaluate the effects of therapeutic measures designed to minimize the mass of infarcted tissue. Approaches which must be explored include manipulation of factors determining preload, afterload, myocardial blood flow and cellular metabolism. In the evaluation of infarct size, isotope methods, methods of electrocardiographic mapping, and enzyme liberation should be examined. These techniques would also be used to explore the



exciting potential of surgical therapy in the treatment of either angina or myocardial infarction. Sharply defined subsets of patients could be randomized into medical and surgical groups.

2.2.12 Artificial Heart and Transplantation

It is recognized that there will always be certain patients with irretrievably damaged hearts, and for these patients total replacement would appear to be the only solution. This could also be true for other disease categories such as cardiomyopathy. Two routes were explored: that of transplantation of the heart from a cadaver or from a lower primate and the implantation of a totally mechanical heart. The problem of donor availability for cadaver transplants appears to be great and resistant to solution, and there is limited promise for the transplantation of hearts from lower animals although the latter approach may become attractive with further progress in transplantation immunology. More certain, however, would appear to be the development of a totally mechanical heart. The major problem in this area appears to be the development of an appropriate surface which is compatible with blood. The problems of circulatory regulation, power transfer and heat dissipation appear to be amenable to solution.

2.2.13 Emergency Medical Services

Available for immediate application are the techniques of emergency medical care. The objectives should be the delivery outside the coronary care unit of the methods of arrhythmia control and cardiac resuscitation which are known to be effective within the coronary care unit. There is need for

widespread education of the public in the fundamental technique of cardiopulmonary resuscitation. The public must also know when and how to call the emergency service and the service must respond promptly. The system must be designed for the area it serves with specialized vehicles and in some situations helicopters would be desirable. The system for the delivery of emergency cardiac care must be a part of a comprehensive emergency care system designed to provide optimal management for all types of emergencies. This obviously requires widespread education, communication and the training of personnel at various levels from the general public through paramedical persons, nurses, and physicians. Patients at high risk and their families should be instructed to avoid delay between the onset of premonitory symptoms and the seeking of medical aid. The families should also receive special instruction in resuscitation procedures. There is also need for equipment such as cheaper instruments for defibrillation, ECG recording, and transmission of ECG information from the mobile unit to the hospital for special consultation.

2.2.14 Primary and Secondary Prevention and Rehabilitation

Primary prevention of coronary heart disease in patients without prior clinical disease is similar to secondary prevention of a second attack in a patient who has already had one event. This country is far behind others in the development of techniques for community screening, testing, registration and follow-up of the potentially diseased person. The rehabilitation of individuals with coronary disease on the basis of physiological, psychological and sociological approaches deserves emphasis. The rehabilitation process



needs to be evaluated with quantification of the effect of the various components. This must be supplemented by the development of demonstration units in which patients with myocardial infarction can be subjected to organized programs of exercise and psychological reinforcement, and thereby returned to useful life.

2.2.15 Recommendations

The recommendations of the Task Group on Coronary Heart Disease were that support be provided for projects in the following areas:

1. Conduct studies concerned with the prevention of coronary atherosclerosis and hypertension. (See 2.1 and 2.4)
2. Study the mechanism of action of factors which precipitate myocardial ischemia, acute myocardial infarction, and sudden death, including studies of the interface between flowing blood and vessel wall, development of collateral circulation, regulation of blood flow, and drug action on the interaction between the vessel wall and flowing blood.
3. Study the metabolic, mechanical and electrophysiological properties of the ischemic myocardium with special attention to the pathogenesis of arrhythmias and the protection of the ischemic myocardium.
4. Develop an animal model for myocardial infarction, sudden death and arrhythmia due to coronary arterial disease to expedite and accelerate progress with regard to the development and testing of preventive and therapeutic agents, devices and surgical procedures.
5. Develop simple, safe, rapid, noninvasive methods for the detection and quantification of coronary atherosclerosis.



6. Develop techniques for the quantification of myocardial ischemia which could be used in trials of medical and surgical therapy.
7. Evaluate currently available methods of therapy, for example antiarrhythmic prophylaxis, drug therapy, for angina pectoris and myocardial infarction, and surgical therapy for angina pectoris.
8. Improve methods of providing emergency medical services including public education concerning the early warning symptoms of ischemic heart disease and widespread training in basic resuscitation procedures. Patients known to be at high risk, and their families, should be given specific instruction concerning the avoidance of the delay between the onset of premonitory symptoms and the seeking of medical aid. A coordinated community emergency service should include a transportation and communication system and associated life support stations.
9. Improve the rehabilitation of cardiac patients which depends upon the education of physicians, industry, insurance companies, compensation boards, and the general public. These groups must learn that most patients with coronary heart disease can return to work and that cardiac function can be determined by objective tests and utilized in making work recommendations.



PERIPHERAL VASCULAR DISEASE

2.3.1 Definition and Scope

Approximately 265,000 patients are discharged each year from hospitals with the primary diagnosis of peripheral vascular disease and in an additional 800,000 persons, peripheral vascular disease is listed as a secondary diagnosis. Thus, although not a prominent cause of mortality, peripheral vascular disease is an important cause of morbidity in the United States today. Intermittent claudication and ulceration of the skin of the extremities interfere with locomotion, and hence limit the productivity of men and women who must move about in order to work.

2.3.2 Fundamental Atherosclerosis Research

Atherosclerosis is the major cause of peripheral arterial insufficiency, and therefore, research directed at the prevention or amelioration of the atherosclerotic process is of fundamental importance. Also of value in this area are studies designed to provide a better understanding of the neural control of vascular tone and of blood flow in the limbs. An understanding of the mechanism of action of smooth muscle in the blood vessel wall would encourage the development of drugs and studies of drug action which could increase peripheral blood flow.



2.3.3 Contributory Risk Factors

Hypertension, diabetes mellitus, smoking and obesity increase the peripheral vascular complications of atherosclerosis. The early detection of patients with peripheral vascular insufficiency, especially in these high-risk groups, would be important since modification of these risk factors would presumably reduce morbidity. There is need for the development of improved methods to detect peripheral vascular disease early in its course. Noninvasive techniques using ultrasound or possible radioisotopes are worthy of intensive study.

2.3.4 Therapeutic Measures

Surgical reconstruction is possible in many cases in which large vessels are involved. However, prosthetic grafts in vessels less than 5mm in diameter, or in vessels where the graft extends across a body joint, are less effective and frequently become occluded. There is need for research directed at the improvement of prosthetic materials with emphasis on surfaces which are compatible with the circulating blood. The ideal arterial substitute has not as yet been developed. Additional investigative approaches should be directed toward measures to increase collateral flow such as exercise programs, alteration of vascular reactivity, and to the development of drugs designed to reduce the tendency for platelet aggregation and clotting.

The careful evaluation of any therapeutic measure, medical or surgical, depends to a large extent upon improved methods for the quantification of the abnormality, so that improvement can be measured. There is need for a unified standard



system for the classification and identification of peripheral vascular disease states and for methods of recording results of therapy from a variety of centers.

2.3.5 Other Peripheral Vascular Conditions

Other peripheral vascular conditions, such as Buerger's disease and various vasospastic conditions, although relatively rare in comparison to atherosclerosis, should be studied. Research in this area might produce information about the neural control of the circulation which could be applied to the therapy of atherosclerotic peripheral vascular disease.

2.3.6 Need for Special Training

The extreme shortage of trained people in this field is emphasized. There are very few vascular specialists in this country; hence, the rate of progress in investigation in this field is slow. It is suggested that medical school and post-graduate training programs in cardiovascular disease be encouraged to include peripheral vascular studies in their curriculum. Training and research programs in peripheral vascular disease should be encouraged and the possibility of various incentive awards as suggested in the report of the NHLI Panel on Peripheral Vascular Disease should be considered. An increase in the number of people dedicated to this particular disease problem would result in a decrease in the morbidity attributable to peripheral vascular disease and also would probably contribute to more rapid progress in clinical investigations.

2.3.7 Recommendations

The recommendations of the Task Group are:

1. Determine how to prevent the development of atherosclerosis of peripheral vessels (2.1).
2. Develop noninvasive techniques for the localization of atherosclerotic lesions, quantification of their severity and the measurement of blood flow.
3. Develop improved prosthetic or biological vascular substitutes.
4. Determine the mechanisms which control the development of collateral circulation. Study the factors which regulate vascular smooth muscle. Determine the sites of action of vasoactive drugs.
5. Determine the mechanism by which diabetes, smoking, and hypertension promote the atherosclerotic process in peripheral vessels.
6. Standardize nomenclature and treatment programs by characterizing the extent, location, and type of disease with respect to therapy. Cooperative trials would be facilitated by this standardization.
7. Develop trained specialists (such as clinicians, allied health professionals, and basic investigators) in peripheral vascular disease to work as teams in medical centers and thus improve education and delivery of care.
8. Establish definite criteria for rehabilitation and job retraining for those afflicted with peripheral vascular disease. Identify occupational factors that might be important in retarding progression of peripheral vascular disease: environmental temperature, position or motion requirements of a particular job, etc. Early detection of peripheral vascular disease and patient education regarding disease management are the main rehabilitation components.
9. Begin national efforts through public education regarding both the early signs of peripheral vascular disease and relevant risk factors.

2.4 HYPERTENSION

2.4.1 Introduction

It has been estimated that 15 percent of adult Americans have hypertension, and among the black population the prevalence may be twice as great. Only half the persons who have hypertension are aware that they have the disease. High blood pressure is associated with a reduced life expectancy due to an increase in the frequency of stroke, heart attack, heart failure, and kidney failure. The basic cause or causes of hypertension remain unknown. However, recent evidence indicates that effective treatment of hypertension by drugs will reduce the incidence of stroke, major vascular complications, and heart and kidney failure. Despite this information about the efficacy of treatment, it is estimated that less than one in five patients with hypertension are currently receiving adequate therapy.

There is need for a balanced approach which encompasses investigation into the pathogenesis and physiology of hypertension and also includes clinical trials of drug therapy and demonstration programs to apply the information already available.

2.4.2 Etiology and Pathogenesis of Hypertension

Nine areas for investigation were identified:

Genetic Factors

The high incidence of hypertension in blacks suggests that genetic factors may be important. Among whites, hypertension

definitely occurs in families and appears to have a strong hereditary aspect. An exciting possibility would be the identification of a genetic marker that would identify the prehypertensive patient so that appropriate therapy could be instituted prior to the onset of clinical disease.

Kidney

For more than 150 years the kidney has been invoked in the cause of hypertension, but the precise mechanism by which it induces hypertension has been obscured. There is increasing evidence that renin and angiotensin are involved in many and perhaps in all forms of hypertension; further, there is considerable evidence that the kidney has not only a hypertension-promoting function, but also an antihypertensive (hypertension inhibiting) function. Recently, the prostaglandins and other special lipids have been considered as possibly playing a role in this action. It is possible that changes in renal blood flow and intrarenal pressure, differences in renal innervation, and change in renal mass and in mechanisms for sodium excretion all contribute to the development of hypertension. The kidney probably plays such a central role in hypertension that any condition that affects its function, whether it be infection, autoimmune disease, chemicals or vascular disease can play an individual or participate in a collective role in the subsequent development of hypertension. The well-known "vicious cycle" in hypertension is evidence of the central role of the kidney: Hypertension can so damage the kidney that an exacerbation in hypertension results which, in turn, further damages the kidney. On the other hand, the cycle may begin at the other end, namely in the kidney, with primary kidney disease, which



produces hypertension, which in turn produces further kidney damage, with the cycle being further exacerbated. A study of all forms of renal disease is relevant. Fortunately, there are some well-established animal models that can replicate the hypertensive states that prevail in man, and therefore they will be most useful in delineating basic mechanism.

Adrenal Cortex

The adrenal cortex should be the target of additional investigation in that the mechanism whereby mineralocorticoids produce hypertension remains unknown. This has therapeutic potential in that drugs which antagonize the action of aldosterone have already been proven to be useful in the treatment of hypertension.

Dietary Salt

It is possible that the excess salt in the diet of Americans may play a role in the genesis of the hypertension which is so common among blacks. The relationship of salt to hypertension needs further clarification. Suggestive evidence includes the observation of the high salt content of the diet in northern Japan which is associated with a very high incidence of hypertension. Baby foods in the U.S.A. have a very high salt content. Much effort should be made to find the link between a high salt intake and hypertension. Feeding salt to rats produces hypertension only in certain genetically susceptible strains. The possibility that the same principle may well be true for man requires further investigation. The interplay of psychological, social and environmental factors is also important.



Autonomic Nervous System

The autonomic nervous system undoubtedly plays a central role in hypertension. Manipulation of the autonomic nervous system with blocking agents and other drugs has been very effective in lowering elevated blood pressure levels. Hypertension in man could be the result of a genetically induced lack of coordination of the autonomic system and this possibility should be investigated.

Cardiovascular Hemodynamics

Attention should be directed to basic studies of cardiovascular hemodynamics with special emphasis on the regulatory systems which maintain blood pressure and cardiac output. It is possible that a derangement in this system may be responsible for hypertension. A high intake of sodium may accentuate this derangement in genetically susceptible individuals.

Female Sex Hormones

Female sex hormones are undoubtedly important as evidenced by hypertensive toxemia of pregnancy and the recently described hypertension associated with the use of the contraceptive pill. Studies of the mechanism whereby the estrogens and/or progestinal compounds produce hypertension would provide further insight into the general mechanism of the generation of hypertension.



Arterial Smooth Muscle

The need for basic studies of arterial smooth muscle should also be emphasized. The level of the blood pressure is dependent upon the diameter of the lumen of small blood vessels, the walls of which consist almost exclusively of vascular smooth muscle. A better understanding of the process of contraction and relaxation of smooth muscle would have far-reaching implications with regard to the control and treatment of hypertension. The role and mechanisms of hypertrophy of this smooth muscle are also important areas for investigation.

Obesity

Obesity somehow strongly predisposes to essential hypertension. The mechanism responsible for this association should be studied.

2.4.3 Detection, Diagnosis and Treatment of Hypertension

Although the etiology and pathogenesis of hypertension remain to be determined, there are diagnostic and treatment modalities which have proven to be useful. Although such treatments may not cure the disease, it has been demonstrated that they prevent major life-threatening complications. Therefore, it is essential that simultaneous with the performance of fundamental studies, effort be applied to improving the diagnosis and therapy of the patient with hypertension.

Studies of the mode of action of antihypertensive drugs should be pursued vigorously. While currently available

drugs are effective, none of those now available is completely satisfactory. The development of new drugs with longer duration action and fewer side effects should be encouraged. A preferred drug would lower blood pressure when taken once a day, and would not be inordinately expensive. The best combination of presently available drugs should also be sought. Individual drugs should be compared for relative efficacy. The mode of action of the several classes of antihypertensive drugs now in use is still somewhat indefinite; more knowledge would undoubtedly improve treatment.

Preliminary evidence suggests that intensive treatment of high blood pressure in patients with coronary heart disease may be associated with a significantly lower overall mortality rate and a lower specific mortality from coronary disease. Because of their great potential significance, these observations require confirmation.

Furthermore, it must be determined:

- What are the best forms of treatment for patients with different kinds and degrees of kidney disease?
- What is the best therapy for so-called hypertensive crises?
- Should primarily systolic hypertension be treated?
- Do patients with borderline hypertension, however defined, benefit from treatment?
- Is hypertension reversible by sufficiently early diagnosis and long periods of maintenance of blood pressure at normal levels?



Finally, and perhaps most important, the effect of anti-hypertensive therapy on the emergence and progression of coronary artery disease must be determined. The mechanism by which hypertension accelerates atherosclerosis in the coronary and cerebral arteries is also an important area for study.

The detection of hypertension is an important area for immediate action. The problem of determining whether a mild and casual elevation of the blood pressure in a young person connotes the future development of chronic blood pressure elevation is important but unsolved. In particular, it would be of value to observe carefully the long-term progression of blood pressure in pubertal (13 year old) adolescents who are in the upper sixth of the population with regard to arterial blood pressure. Appropriate drug intervention in this group could tremendously reduce stroke and coronary disease. However, only careful long-term observations will identify the most appropriate antihypertensive measures.

A few forms of hypertension, especially those due to renal vascular disease, are curable by surgical techniques; and early detection before irremedial vascular disease occurs is mandatory. There is need to develop a minimum-effort/maximum-effectiveness procedure which can be applied to large numbers of patients to detect those who may benefit from surgical therapy.

An aid in the study of hypertensive patients would be a method for the frequent recording of ambulatory blood pressure.

Much must be done in the area of professional and public education. Doctors must be made to recognize the importance of treatment of hypertension, and the public has to recognize the value of treatment and be willing to persist faithfully while an optimum drug schedule is being worked out. This is the price which must be paid for long-term benefit.

The application of basic knowledge for the benefit of the general public must take place in an orderly manner; and the development of an effective system of antihypertensive therapy requires research into the modes of delivery of care. Studies are needed to determine the effectiveness of special nurses and other allied health professionals in the management of patients with hypertension. The best methods for educating and motivating patients must be determined. Various systems for implementing these objectives need to be evaluated. The application of tested delivery systems must be utilized first in discrete local model programs to determine optimal logistical approaches in a field trial setting. Only then should general application of the most effective system of delivery be applied to the general public.

It is urgently desired to apply the information already at hand to identify and treat that large population of hypertensive patients (more than 80 percent) who are not at present receiving adequate treatment. Early detection of hypertension, patient education, and treatment to prevent the complications of hypertension are the main rehabilitative efforts for patients with this disease. Such a program requires considerable planning before successful implementation is possible.



This includes:

- Physician education
- Public education
- Training of allied health specialists in hypertension to handle the massive problem of detection, diagnosis, and treatment
- Developing systems for effective hypertension care delivery for different population groups. Such care requires the lifelong cooperation of the patient. Means should be sought to encourage such cooperation.

The climate for drug review and evaluation must be improved so that industry and medical scientists will be encouraged to develop new antihypertensive drugs. At the present time, antihypertensive drugs are available in Europe which cannot be used in the United States.

Elevation of blood pressure is the major cause of hemorrhagic stroke, congestive heart failure, kidney failure, malignant hypertension, encephalopathy, stroke from closure of a brain artery, and dissecting aneurysm of the aorta. It is also a major predisposing factor for heart attack. Since it is difficult to envision applying present methods of treatment to all those who require them, it is imperative that massive support be given to efforts to discover the causes of hypertension. Elucidation of the causes of hypertension offers the greatest promise for complete control and prevention of the disease.



2.4.4 Recommendations

A dual approach is recommended:

- To effectively apply what is already known in broad-scale treatment programs
- To simultaneously expand research in well-defined and promising areas which seem likely to expose causal mechanisms and lead to even better drug treatment.

Specific recommendations are as follows:

1. Educate physicians, special nurses, health care personnel and the general public in the great value of thorough, persistent, and skillful treatment of hypertension, then develop optimal methods for bringing large numbers of hypertensive patients under adequate, continuous, long-term treatment.
2. Develop and facilitate the release of better drugs to combat hypertension and provide assistance as needed to the Food and Drug Administration to attain this goal.
3. Determine an efficient system of mass screening for early asymptomatic hypertension and for "prehypertension" in teenagers. Therapeutic trials with regard to treatment of borderline hypertension are also needed. The effect on stroke, coronary heart disease, and sudden death should be particularly noted.
4. Train physicians, special nurses, and scientists to accomplish the research and treatment objectives of the hypertension problem.
5. Study the kidney as a regulator of arterial pressure, including the role of the renin-angiotensin-aldosterone system and how it meshes with the central and autonomic nervous systems in the total regulation of blood pressure and cardiac output. The effect of decreased renal mass on arterial pressure is another question to be addressed.



6. Study intrarenal pressures, flows, and the distribution of pressures and flows that constitute signals for regulation of the secretion of various renal hormones--both pro- and antihypertensive, including renin, prostaglandin, kallikrein, other lipid materials, etc.
7. Study the interrelationship of plasma volume, extracellular fluid volume, cardiac output, sodium intake and output and adrenal and other hormones as they relate to the narrowed arterioles encountered in hypertension. Determine why thiazide diuretics, spironolactone and beta-adrenergic blocking drugs decrease arterial pressure.
8. Study the pathophysiology of vascular smooth muscle in hypertension.
9. Determine how hypertension "begets" hypertension, exploration of the "vicious cycle" aspect of hypertension and the means for breaking it.
10. Determine why hypertension leads to an acceleration of atherosclerosis in the cerebral and coronary arteries and why it predisposes to intracerebral hemorrhage.
11. Conduct epidemiological and clinical studies of the genetic, constitutional and environmental factors of importance in hypertension.
12. Determine why hypertension causes changes in the arteriolar wall and the pathophysiologic consequences of these changes. This problem should be studied in diabetic as well as nondiabetic patients.
13. Study the relationship of endogenous mineralocorticoids to hypertension.



2.5 STROKE

2.5.1 Background

Approximately 200,000 deaths each year are attributed to stroke in the United States. Cerebral infarction is the most common type of stroke, accounting for 70 to 80 percent of this total. The mortality rates are much higher in blacks than in whites and in men than in women under the age of 65. The death rate increases strikingly with advancing age. There are about 530,000 discharges each year from hospitals because of stroke, and about 250,000 individuals between age 25 and 64 are disabled by a stroke.

Some striking racial and environmental differences in the incidence of stroke may provide useful clues for further investigation. For example, stroke death rates are very high in Japan, but Japanese who have migrated to Hawaii and California have substantially lower death rates than the Japanese in Japan. There are also great differences in stroke death rates within the United States, with the highest rates being found in the southeastern United States, especially along the Piedmont Plateau.

2.5.2 Approaches

Probably the best approach to stroke is to consider (1) the factors that lead to a stroke, (2) the factors that influence the survivorship and disability during a stroke and (3) the determinants of long-term disability and death following a stroke.



2.3.3 Prestroke Factors

Hypertension

The research of the past 10 years has clearly shown that elevated blood pressure is the cardinal risk factor for stroke. The great majority of stroke patients have pre-existing hypertension. Furthermore, there is conclusive evidence that the treatment of patients with moderately to markedly elevated blood pressure will substantially decrease the risk of stroke, especially that due to cerebral hemorrhage. This relationship between hypertension and stroke, established in the case of severe hypertension, must be investigated in a population of mildly hypertensive patients. This is of great importance because the majority of the 23 million persons with elevated blood pressure have only mild elevations. Clinical trials of antihypertensive therapy in patients with mild hypertension are therefore needed.

Even if the trials of antihypertensive therapy in patients with mild hypertension show a beneficial effect of therapy, the problem of long-term antihypertensive therapy in this group will be great. For example, it is unlikely that 23 million people, many of whom are asymptomatic, can be maintained on antihypertensive therapy for the rest of their lives. The side effects, cost, and the potential long-term hazards of therapy make drug therapy an impractical long-range solution. A better approach would be the prevention of hypertension through better understanding of its etiology and pathogenesis.

Several important clues to the etiology and prevention of hypertension, available from prior studies, need further expansion. Blood pressure is much higher in blacks than in whites, and there is suggestive evidence of both genetic and environmental factors that account for these differences. For example, recent studies have suggested that there is a marked social class gradient in blood pressure among blacks, with lower social class individuals having higher blood pressure than upper social class individuals. On the other hand, preliminary studies have noted that high blood pressure is also common among blacks in Africa and South America suggesting genetic components. These studies must be expanded and supplemented by research on the pathophysiological differences in blood pressure regulation between blacks and whites.

Obesity

Obesity is another factor that is related to elevated blood pressure. Obesity and weight gain over time increase the risk of hypertension, especially among women. There is a need, therefore, to determine the interrelationship of dietary factors, genetic and pathophysiological mechanisms in obesity. Also, the natural history of high blood pressure in obese, as compared with nonobese, individuals should be evaluated.

Hyperglycemia

A second major risk factor prior to stroke is abnormal carbohydrate metabolism, as manifest by hyperglycemia, hypoinsulinemia and clinical diabetes. The risk of stroke



is high among diabetic patients and there is also a strong correlation between obesity, hyperglycemia, abnormal insulin response to glucose load and hypertension. Part of the interrelationship of diabetes with stroke may be through these correlations. In certain populations, hyperglycemia may not be associated with an increased risk of vascular disease, but these populations are generally categorized as having a low total fat and caloric intake and may have a different variant of hyperglycemia. Current therapeutic approaches to the treatment of hyperglycemia in adults are unrewarding and newer approaches have to be developed.

The interrelationship of hormonal factors in obesity, hypertension, hyperglycemia and hypertriglyceridemia should be explored. There is a possibility that all these factors are related to a common endocrine imbalance, and the emergence of these metabolic abnormalities in childhood deserves further study. The development of animal models would also be helpful. Basic research in endocrinology and neurohumoral interrelationships would be important to the solution of the stroke problem.

Other Risk Factors

The relationship of other atherosclerosis risk factors (e.g., serum lipid levels, cigarette smoking, and uric acid) to stroke is less clear than it is to coronary artery disease. Further research to describe the relationship of specific risk factors to the topographical distribution of atherosclerotic disease in the different vascular beds should receive high priority.

Aging

The magnitude of the risk factors related to stroke, such as blood pressure, blood sugar and serum lipids, increases with advancing chronological age. The incidence of stroke also markedly increases with age, doubling with every seven years of increase in chronological age from middle age onward. Conceivably, at least part of the association of the risk factors with stroke is a measure of biologic aging. Thus, individuals who age more rapidly in a biologic sense may have risk factors of greater magnitude and hence an increased risk of stroke. The accelerated aging process could reflect some nonspecific environmental agent such as radiation exposure, exposure to chemical or air pollution, etc., or could be genetically determined.

Vascular Disease

The basic pathology of occlusive stroke disease is atherosclerosis of the extracranial or intracranial arteries or atherosclerosis of the small intracerebral arteries. In general, the atherosclerotic disease is diffuse and involves more than one artery. Stenosis of an artery of less than 70 percent is generally not considered to be associated with substantial reduction of cerebral blood flow. One of the major drawbacks to the proper understanding of the interrelationships between arterial disease and stroke has been the failure of techniques to measure the degree, type and site of arterial disease in asymptomatic individuals by methods that are safe, accurate, reproducible and applicable in the screening of large populations. With such techniques, it would be possible to identify and focus preventive efforts



on the high risk groups. For example, a method whereby vascular disease, such as microaneurysms, could be identified among individuals with elevated blood pressure would open many fruitful avenues for investigation. Studies in such a population would result in better understanding of the relationship between elevated blood pressure, other risk factors, and vascular disease. The relationship between vascular disease and subsequent stroke could be determined. A more rational approach to surgical therapy for extracranial arterial diseases would be possible. The value of drugs thought to either reduce or inhibit further development of atherosclerosis could be assessed.

Contrast angiography is the most accurate method of evaluating the cranial circulation but its application is limited because it is not safe enough for widespread use. The evaluation of risk factors, of new therapy and of the natural history of cerebral vascular disease will depend to a large extent upon the ability to identify asymptomatic disease in patients and on the better localization of lesions in these patients, as well as in patients with symptoms.

Thrombosis and Embolization

Thrombosis and embolization have been considered to be of importance in occlusive cerebral vascular disease for two reasons:

- Thrombogenesis may be of considerable importance in the actual development of the atherosclerotic plaque and consequent narrowing of the artery.



- The formation of a thrombus and subsequent embolization from an atherosclerotic plaque in an artery in the chest or neck may result in transient ischemic attacks or a completed stroke.

The relationship between thrombosis, embolization and transient ischemic attacks and strokes is perhaps unique to the stroke problem and requires intensive study. The major problem, at present, is the need for a method for the in vivo identification of thrombi in the carotid arteries prior to and after embolization. Thus, the highest priority should be given to tests which will permit thrombi and microembolization to be identified in vivo.

Transient Ischemic Attacks (TIA)

Many individuals have episodes of transient cerebral ischemia prior to a stroke. The exact pathogenesis of these TIA's and their relationship to subsequent stroke needs further evaluation. At present there is no diagnostic test prior to a stroke which can be used safely to identify high-risk individuals. The simplest noninvasive techniques include the following: questionnaires to elicit a history of symptoms suggestive of transient ischemic attacks; thermography; ultrasound; and pulsewave propagation techniques. The evaluation of all of these techniques has been difficult because of the absence of any objective technique for comparison purposes and the limited utilization of noninvasive methods in asymptomatic individuals. Many of the tests have been found to be predictive in patients with a completed stroke or extensive vascular disease, but their value as screening or diagnostic techniques prior to stroke in the general population has not been determined. Newer types of instrumentation and the evaluation of their efficacy are needed.

An idealized approach to the asymptomatic or early symptomatic patients might be organized as follows:

- Identification of high-risk subjects such as those with hypertension, diabetes or atherosclerotic heart disease.
- Questionnaires would be completed by these high-risk subjects to identify symptoms suggestive of cerebral vascular disease.
- Those with suggestive symptoms would be subjected to noninvasive testing to localize extracranial disease.
- Radioisotope techniques to evaluate extracranial disease and possibly intracranial disease.
- Patients with positive results on noninvasive and radioisotope studies would have angiographic procedures.
- Medical or surgical therapy would be based on the results of these tests and on clinical trials of the efficacy of therapy.

2.5.4 Important Factors During a Stroke

The risk factors that determine the survivorship and subsequent disability during a stroke are much less clearly understood than those prior to a stroke, but are probably of less importance. The factors influencing the course of the stroke patient include the risk factors, such as hypertension, which were present prior to stroke and which may further influence the course of the acute stroke; the pathophysiological changes in the cerebral infarct and in the surrounding brain are important. The factors that influence cerebral blood flow prior to and during a stroke have to be

determined. The role of vasospasm in the cerebral vessels requires further definition. Studies of the metabolic derangements in the brain during stroke might also prove to be rewarding. The factors which contribute to the irreversibility of brain damage also require elucidation. For example, brain tissue subjected to ischemia does not show enhanced de novo synthesis of adenine nucleotides (ATP) whereas similarly challenged heart and kidney show a markedly increased synthesis. Metabolic and pathophysiologic changes in other parts of the body as a consequence of stroke cannot be ignored. The understanding of these metabolic factors during a stroke would make it possible to develop a more rational approach to stroke care, including the evaluation of therapeutic agents, standardization of care (special treatment facilities, community hospitals, home care, etc.) and might decrease the duration of hospitalization for the patient judged to be at low risk. The answers to all these questions will require large cooperative studies involving many disciplines including basic science, physics, chemistry, and engineering. Developments of instruments and techniques for early detection of cerebral vascular disease will be the key to success of the program.

2.5.5 Therapy During Acute Stroke

The approach to therapy during a stroke depends on the answers to four key questions. First, it must be determined whether or not specialized intensive stroke care reduces the mortality and morbidity of stroke below that to be expected from standard hospital care.

The second major question concerns the efficacy of the combination of short-term hospitalization and home care in managing the stroke patient. The effect of a program consisting of a few days of hospitalization followed by specialized home care must be studied. The home care program would require training of health care professionals to work with the patient's family in implementing the scheduled program.

The third question concerns the possibility of treating stroke patients without hospitalization. Such a plan would involve evaluation in a special outpatient stroke center or emergency room followed by home care supervised by home care physicians assisted by trained health care professionals including nurses and rehabilitation specialists. Programs of this sort have been successfully implemented in other countries.

The fourth question concerns the design, organization, and utilization of a chronic long-term facility for the treatment of the stroke patient after the acute phase of illness and the appropriate timing of transfer to such a facility. It is possible that the best plan would be a few days of acute care in a facility oriented toward rehabilitation, followed by long-term care in a second specialized facility. This plan would contrast with the current plan in which relatively long-term care is carried out in a single acute care facility.

All of these approaches will require (1) careful evaluation, (2) the development and training of new types of personnel



both within the hospital and within the community, and (3) educational programs for the patient's families and perhaps for patients themselves.

2.5.6 Factors of Importance After a Stroke

The factors which determine the long-term prognosis after a stroke include the degree of impairment which follows the initial stroke, the host factors such as age, and the presence of other disease, especially cardiovascular and peripheral vascular diseases. The same risk factors that were related to the initial stroke, such as hypertension, diabetes, and blood lipid abnormalities, are quite possibly also of importance. Many patients who survive the initial stroke ultimately die of cardiac disease rather than recurrent stroke or of the impairment associated with the initial stroke. For this reason careful evaluation of the cardiac status of stroke patients is of great importance.

The best approach to the rehabilitation of the stroke patient must be determined. For example, it is not known whether organized stroke rehabilitation programs offer a better outcome than routine good care within the community. Furthermore, the types of individuals (training and background) who would be involved in a rehabilitation program and the facilities necessary for a good rehabilitation program have to be developed and evaluated. A major problem in this area is the lack of standardized diagnostic methods to evaluate the impairment after stroke. This has been discussed in the section on diagnostic methods. The approaches to the specific impairments related to stroke, such as aphasia, hemiplegia,

and various sensory deprivations have to be carefully evaluated. The benefit of rehabilitative procedures on each specific impairment has to be measured with special attention to the duration of therapy which is required. The planning for facilities, personnel, and equipment should be based on such measurements. The best approach must be found for the preservation and possible enhancement of limited function at a reasonable cost in patients with severe impairment.

The natural history of stroke following hospitalization, with clinical trials to evaluate different modalities of rehabilitation therapy, should be studied. Since most patients who have had a stroke will be outside of the hospital, and perhaps not even visited by a physician, the training of other health care personnel in the evaluation of impairment after a stroke should be considered. Standardized procedures for measuring this impairment will have to be developed prior to the evaluation of any rehabilitation effort. It may be necessary to coordinate the rehabilitation programs into an integrated stroke effort rather than having separate rehabilitation programs in the community, as is currently the practice. Unfortunately, research into the evaluation and development of rehabilitative procedures has lagged far behind research efforts in other areas related to cerebral vascular disease.

2.5.7 Recommendations

Research on stroke should focus on the following areas:

1. Determine the etiology and prevention of hypertension. (See 2.4)
2. Improve methods for the diagnosis and long-term treatment of the hypertensive patient. (See 2.4)
3. Develop methods that can be used in the population for the early identification of the stroke-prone individual and especially for a better understanding of the identification, pathogenesis and treatment of transient cerebral ischemia.
4. Investigate the pathophysiological and biochemical changes at the cellular and subcellular level attributable to stroke, so that more effective therapeutic measures can be planned.
5. Evaluate the interrelationship of thrombosis and embolization to the atherosclerotic process and the development of stroke and transient ischemic attack. Specific studies to determine the relationship between ulcerated atherosclerotic plaques, embolization and subsequent transient ischemic episodes and stroke, as well as the possible development of therapeutic modalities to prevent embolization, should receive high priority. (See Blood Diseases Panel Report)
6. Support scientific evaluation of the best types of acute stroke care and rehabilitation. The determinants of recovery and of successful rehabilitation must be identified. Considering the large sums of money spent for stroke care, the absence of solid scientific evaluation is deplorable. Evaluation of optimal methods of re-training patients both for work and for independent living after stroke are needed.
7. Develop a good animal model of cerebral atherosclerosis and stroke.



Congenital heart disease is an abnormality of the heart and blood vessels with which a child is born.

It is estimated that eight of every 1,000 newborn infants have congenital heart disease. The importance of this disease is probably underestimated in that it is not known how many spontaneous abortions occur as a result of congenital heart disease which has developed in the fetus. Half of the children born with congenital heart disease do not reach their first birthday, and 90 percent of the half who die in the first year do so within the first six months of life, and most of these by the third month. Thus, the neonatal period is the time of greatest risk.

More than 90 percent of all congenital cardiac anomalies can be corrected or palliated, and if this is accomplished early in life, normal function is often restored and the individual will have a near normal life span and productivity. These facts are of importance in considering the relative significance of advances in the treatment of congenital heart disease as compared with other forms of heart disease which primarily attack the adult in middle life or later. Therefore, although the incidence is relatively small, the yield to be expected from early detection and treatment of congenital heart disease will be great when measured in terms of years of productive life.

Four major aspects to the program were recommended by the Task Group:

- Studies of the etiology and pathogenesis of congenital heart disease as related to its prevention
- Improved detection and diagnosis of congenital heart disease
- Treatment of congenital heart disease and subsequent rehabilitation
- Education and training.

2.6.2 Etiology and Pathogenesis

High priority should be given to studies designed to prevent the malformation before it occurs. Factors which are known to contribute to the inception and development of congenital heart disease are viral agents, genetic factors and teratogenic agents.

The available approaches for the detection of viral agents which produce congenital heart disease include:

- Serologic studies to document maternal or newborn infections
- Virus isolation from neonatal tissue (autopsy or biopsy)
- Studies of teratogenetic effect of "human" virus infection in animals, preferably primates.

Programs for prevention through the use of vaccines or chemotherapy should become available once the significance of viral agents in the production of congenital heart disease is identified.



The understanding of genetic factors in the causation of congenital heart disease will:

- Identify individuals and families at risk,
- Discover environmental factors which act on predisposed individuals, and
- Help in the definition of production of congenital cardiac malformation.

There is a particular need for basic research directed towards the effects of teratogenic agents in congenital heart disease. Knowledge is needed in:

- Elucidating the earliest events in cardiac embryogenesis and teratogenic mechanisms of abnormal development, and
- Determining the effects of hemodynamic disturbances in the developing embryo.

Close scrutiny of drugs with possible teratogenic potential in humans is essential. This will be enhanced by the development of improved animal models for drug testing.

The drug-induced cardiac defects were cited as a promising area for study, and it was suggested that treatment of animals with genetic predisposition toward cardiac abnormalities with teratogenic and other stress-producing drugs during pregnancy would be a profitable avenue for exploration. That this could have direct application towards certain types of cardiac maldevelopment is known, but the precipitating causes are not understood.

Epidemiological studies would also have bearing on the question of pathogenesis. Investigation of natural clusters of congenital heart disease appears indicated. Prospective identification of pregnancy outcome in high-risk populations should receive high priority. High-risk populations include:

- Offspring of parents who have or have had congenital heart disease and/or previous children with cardiac malformations
- Offspring of pregnancy complicated by maternal viral infection
- Offspring of parents exposed to potential teratogens or carcinogens.

The establishment of a human embryo bank will aid immeasurably in the understanding of organ development in man.

2.6.3 Detection and Diagnosis

The objective of this approach is to salvage the large number of infants who die during the first year of life from congenital heart disease. This would be possible by early detection through intensive professional education, development of new instruments, interhospital communication, and transportation of critically ill infant cardiac patients. It is recognized that cardiac catheterization and angiocardiology are not without hazard in infants; and, therefore, noninvasive methods for detection should be emphasized.

Much has to be learned about normal fetal and neonatal cardiovascular function and mechanisms of cardiocirculatory adaptation to perinatal disorders. It is necessary to characterize:

- The intrinsic properties of the embryonic, fetal and neonatal cardiovascular systems and their adaptation to fetal and perinatal disorders,
- The influence of maternal environmental factors on the developing cardiovascular system, and
- The influence of the developing respiratory, renal and central and autonomic nervous systems on the heart and vessels.

The role of the ductus arteriosus in hyaline membrane disease needs elucidation.

Efforts have to be directed toward the diagnosis of congenital heart disease in the fetus. Avenues to be explored include amniocentesis and noninvasive techniques such as echocardiography. Methods of predicting and preventing pulmonary vascular disease in congenital heart disease are needed urgently.

2.6.4 Treatment and Rehabilitation

The achievements of the last two decades in perfecting surgical treatment for congenital heart disease have been cited. However, the period of highest mortality is still the first few months of life, and better methods are required to bring the benefits of cardiac surgery to the small infant. Attention also must be directed to the long-term "natural history" of patients who have had so-called

corrective operations for congenital heart disease. It is recognized that late arrhythmias are not uncommon and that sudden death may occur. Attention should be given to the habilitation and rehabilitation of patients with operated and unoperated congenital heart defects. More careful attention to the patient's cardiac function before and after surgery would lead to a better evaluation of patient's work, recreational, and vocational capabilities. Emotional and economic problems occurring in patients and their families require investigation.

2.6.5 Education and Training

The final area recommended for attention was that concerned with education and training. There is special need for education of newborn nursery personnel concerning early detection and rapid transfer of babies requiring early cardiac surgery. The first line for detection is usually the nurses and health care personnel working in newborn nurseries. Health care personnel have to be trained to take genetic and teratogenic histories.

Opportunities should be available for the training of biologists in animal teratology. Young scientists need opportunities to train in epidemiology, genetics, teratology, virology and cardiovascular physiology so that these disciplines can be applied to the prevention and treatment of congenital heart disease. Workshops and conferences at which experienced scientists review the principles and concepts in these areas of research have proven effective and stimulating to prospective investigators in other fields.



2.6.6 Recommendations

1. Apply widely currently available diagnostic and therapeutic methodologies, especially in newborn and infants. This entails improved recognition of the disease through intensive professional education and by development of instrumentation for easy detection; improved inter-hospital communication and transportation; and making diagnostic and surgical facilities readily available to treat critically ill infant cardiac patients.
2. Investigate the viral, genetic and teratogenic etiology of congenital heart disease as a basis for prevention.
3. Study the basic mechanism of normal and abnormal cardiovascular function in the fetus and the neonate. These studies are essential since the maturing cardiovascular system differs significantly from that of the adult. These studies would form a background for safer and more effective therapy.
4. Determine the natural and unnatural (postoperative) history of congenital heart disease in order to develop improved indications for therapy and later rehabilitation. Serial assessment of function will aid in patient counselling regarding activity levels, career choice, etc. This will provide information for management of the congenital heart disease patient as an adult, identifying anticipated levels of function, determinants of employability, determinants of insurability, etc.
5. Develop further standard surgical therapy and expand to the problem of the neonate and fetus in utero. The application of surgical correction to these populations is necessary if further reduction in the mortality due to congenital heart disease is to be effected.

This Task Group considered rheumatic fever and rheumatic heart disease, as well as nonrheumatic valvular disease, infective endocarditis and the cardiovascular complications of drug abuse.

2.7.1 Rheumatic Fever/Rheumatic Heart Disease

Rheumatic heart disease is unique among the major cardiovascular diseases in that it is almost completely preventable by currently available diagnostic and therapeutic modalities. Nevertheless, rheumatic fever and rheumatic heart disease still occur with unacceptable frequency.

Antibiotic therapy of streptococcal infections can decrease the incidence of rheumatic fever and shorten the course of the streptococcal illness. Although effective methods for preventing both initial and recurrent episodes of rheumatic fever are currently available, approximately 100,000 new cases of rheumatic fever and rheumatic heart disease occur in the United States each year. More than 15,000 deaths from acute rheumatic fever and chronic rheumatic heart disease were reported in the United States in 1968. More than 100,000 patients are hospitalized annually with a primary diagnosis of rheumatic fever or rheumatic heart disease. The approximate cost of physician care for patients with rheumatic fever and rheumatic heart disease (1969) was \$28,000,000.

However, these figures fail to display the extent of the rheumatic fever problem, because rheumatic fever, unlike most other major forms of heart disease, affects children



and thus is a lifelong disease. Morbidity, not mortality, is the major problem, and disease recurrence with progression of severity is characteristic. Rheumatic fever and rheumatic heart disease can be prevented at relatively moderate cost, precluding the subsequent great expense of management of the chronic disease.

Comparison of current initial rheumatic fever episodes with data from the 1930's indicates only about 30 percent reduction in the attack rate, despite the availability of effective rheumatic fever prophylaxis. Populations with near-optimal medical care (as some Scandinavian countries, U.S. Armed Forces, etc.) demonstrate a far greater decrease in rheumatic fever incidence.

Summary of Approaches

Primary Prevention: Diagnosis and Early Treatment of Beta-Streptococcal Infection

Prompt accurate diagnosis and penicillin treatment of beta-streptococcal sore throat can effectively prevent rheumatic fever episodes. However, prevention of initial rheumatic fever may fail because detection and diagnosis of the streptococcal sore throat may be difficult and these individuals have not been identified as "susceptibles" as have patients with prior rheumatic fever. Extensive implementation of currently available techniques for streptococcal identification is necessary. The development of rapid, simple techniques for streptococcal identification, widely available and reasonable in cost, is urgently needed. A major public and



professional education effort is required regarding the importance of prompt diagnosis and treatment of streptococcal infections in the prevention of rheumatic fever. Identification of motivational factors in patients' adherence to medical recommendations and ways to improve patient motivation must be delineated.

The determinants of rheumatic fever susceptibility, i.e., risk factors, must be identified by careful epidemiologic studies to target preventive efforts toward high-risk groups and/or individuals.

New antistreptococcal antibiotics must be developed and evaluated because of problems of allergy to penicillin therapy and because of the relatively short duration of action of penicillin.

Asymptomatic streptococcal sore throats cannot be identified for treatment. Thus, the only potential means of complete rheumatic fever eradication are by prevention of the occurrence of streptococcal infections by development of a vaccine for group A streptococcus or by the identification and subsequent specific modification of immunologic mechanisms responsible for rheumatic fever occurrence after streptococcal infection.

Secondary Prevention: Prevention of Streptococcal Infection In Rheumatic Subjects

Prevention of streptococcal infections in patients with rheumatic fever/rheumatic heart disease is basic to

prevention of recurrent rheumatic fever (see also "Primary Prevention"), which characteristically increases the severity of the residual heart disease.

The only currently available approach to prevent progression of rheumatic valvular damage is to avoid recurrent episodes of acute rheumatic fever through effective antistreptococcal prophylaxis. Intensive professional and public (patient) education programs regarding the need for adequate prophylaxis must be developed. Factors influencing patient compliance with prophylaxis regimens must be identified, methods developed to evaluate prophylaxis adherence and efforts directed to improve patient motivation for compliance with medical recommendations. Epidemiologic studies are needed to determine the optimal duration and type of prophylaxis, and reasons for failure of prophylaxis regimens. Development of an antistreptococcal vaccine or identification of methods of immunologic intervention would constitute a major breakthrough, with development of alternative, longer-acting antibiotics than those presently used, also being of value.

Management of Patients With Acute Rheumatic Fever and Rheumatic Heart Disease

Effort must be made to improve the management of acute rheumatic fever and to lessen its sequelae.

No specific diagnostic laboratory test or clinical criterion is available to document an initial or recurrent episode of acute rheumatic fever. Availability of improved or specific diagnostic techniques, possibly immunologic indicators, would



be valuable for early accurate rheumatic fever diagnosis, for prompt institution of appropriate treatment, and for the evaluation of prophylactic regimens.

The current management of acute rheumatic fever is effective primarily in shortening the symptomatic phase of the disease, especially the arthritis. Current treatment appears to have little or no effect on the incidence and severity of the residual valvular damage. The role of corticosteroid hormones, of other immunosuppressive agents, of antilymphocyte serum, and of varying amounts and duration of bed rest in altering residual valvular deformity and myocardial dysfunction must be reevaluated in an effort to improve treatment of the acute episode.

Improvement in management of patients with chronic rheumatic heart disease may reduce residual impairment.

Improved intensive professional and public education is requisite for the implementation of currently available knowledge in preventing the complications and sequelae of rheumatic fever, i.e., infective endocarditis, arrhythmias, heart failure, thromboembolic complications, unnecessary invalidism, etc.

Much information is needed regarding:

- Optimal methods and situations for patient education and learning
- Factors influencing patient motivation for adherence to recommended therapy
- Determinants of habit or behavior change, particularly in relation to patient education efforts.



Improved educational methods and communication techniques must be developed for health education and for the delivery of medical care both for adults and children. Psychosocial studies of high-risk population groups, the effectiveness of varied educational and communication techniques and studies on patient adaptation to chronic illness, including motivation for adherence to medical plans, are requisite.

Programs for professional and public education must emphasize the occurrence of acute rheumatic fever, and thus the necessity for disease prevention and detection, in the adult age group. Special problems and their solutions must be identified in the adult female with rheumatic heart disease, such as the selection and safety of contraceptive methods, concerns of pregnancy and obstetrical management, etc.

Better methods must be developed for assessment of valvular and myocardial function, for the prevention and treatment of the complicating bacterial endocarditis and for improved surgical management of chronic rheumatic valvular disease.

Safe, accurate noninvasive techniques (such as exercise stress testing) must be devised to assess cardiovascular function in children and adults. Physicians and health care personnel must be trained to assess functional capacity by exercise stress testing and other noninvasive procedures that can be safely and serially performed, and to establish and relate the identified level of function to occupational and recreational energy requirements and to recommendations for safe activity levels. This assessment, in addition to its use in vocational guidance and in counselling regarding

marriage, pregnancy and childbirth, etc., can identify progressive cardiac function impairment requiring surgical or other modes of intervention.

The "natural history" of surgically treated rheumatic heart disease, including complications of therapy, must be derived.

Comparison should be made of the benefits of surgery, i.e., the long-term results of the various operative procedures, with the operative and post-surgical mortality and morbidity and the uncertain fate of the various prosthetic devices now in use. Criteria for the optimal time of surgical intervention must be defined. Better antithrombotic surfaces must be developed for prosthetic heart valves; newer methods must be investigated to preserve and store homograft valves.

Pathogenesis of Rheumatic Fever

Only a minority of individuals exposed to beta hemolytic streptococcal infection develop acute rheumatic fever. The reason(s) why these individuals develop this abnormal immunologic response is unknown. A thorough examination of the biology of the streptococcus and its modification of the immune response of the host must be carried out in order to understand the pathogenesis of rheumatic fever and thereby devise specific methods for interrupting this process.

Clarification of this altered host-parasite relationship may be obtained by genetic study of susceptible individuals; by an examination of the biologic properties of the group A streptococcus, such as bacterial physiology and morphology, cellular and extracellular antigens and toxins, identification



of antigens which cross-react with mammalian tissue; and a general evaluation of alterations of immune mechanisms in affected individuals. The question of whether or not viral agents act as a cofactor in enhancing susceptibility of individuals to rheumatic fever or whether they themselves are etiologic agents needs elucidation. These examinations of the infective agent and the host response are most likely to provide the data base for development of better diagnostic means, vaccines and specific methods for arresting the disease process through immunologic intervention. Considerable equipment development and research personnel training must supplement this effort. As indicated previously, discovery of such methods will have the greatest impact on prevention of disease or retardation of disease progression.

2.7.2 Cardiovascular Complications of Drug Abuse

This new area of cardiovascular disease needs elucidation of incidence, specific disease problems, morbidity, mortality and recommended therapy--but particularly methods of prevention of the underlying problem, drug abuse. Currently identified cardiovascular complications include:

- Cardiac
 - Infective endocarditis
 - Myocardial disease, primarily alcoholic cardiomyopathy, but other drug cardiomyopathy as well
 - Atherogenesis (presuming that tobacco is considered a drug which is abused)



- Arrhythmias, seen particularly with the phenothiazine drugs which are often prescribed for patients with cardiac disease. Amphetamines may also induce arrhythmias, particularly when more than one drug is abused
 - Pulse and blood pressure abnormalities, seen particularly with marihuana and amphetamine abuse
 - Electrocardiographic abnormalities, primarily with phenothiazine drugs but also with glue sniffing (where hydrocarbons may be responsible for EKG changes, sudden death, arrhythmia and cardiomyopathy)
- Vascular Abnormalities
 - Phlebitis
 - Septic pulmonary embolism
 - Local arteritis
 - Traumatic aneurysm
 - Mycotic aneurysm, both septic and due to methysergide with or without LSD
 - Pulmonary angiothrombosis (talc granulomas)
 - Pulmonary Edema

(Primarily pulmonary edema of respiratory depression, seen mainly with heroin, but also with morphine and Darvon)
 - Effect on the Fetus

An increase in congenital heart disease is seen in babies of mothers taking LSD, amphetamines and other drugs. Enhanced public education as to the cardiovascular risks of drug abuse is needed, as well as physician education in the recognition of these specific disease entities, and recommended therapeutic approaches. Development of animal models would be desirable.

2.7.3 Infective Endocarditis

Public and professional education concerning prevention of infective endocarditis in patients with rheumatic and other causes of valvular disease (and congenital heart disease) is needed. Improved diagnostic and therapeutic regimens for infective endocarditis are needed. Animal models would help evaluate both medical and surgical therapy of infective endocarditis.

2.7.4 Nonrheumatic Valvular Heart Disease

Elucidation of etiology(ies), incidence, natural history and diagnostic methods is needed. Viral infection can serve as a prototype. Evaluation of the role of viral infection in endomyocarditis and chronic valvular disease can be accomplished by epidemiologic and serologic population surveys and by studies of the disease in experimental animal models.

Specific medical and surgical regimens must be delineated, using animal models if necessary. Luetic valvular disease may serve as a prototype approach. Aortic valvulitis secondary to syphilis is one of the more serious complications of this disease and is entirely preventable by the early treatment of primary or secondary syphilis. Continued public education relative to the danger of neglecting diagnosis and treatment of venereal disease is needed. The treatment of luetic aortic regurgitation requires the same considerations as discussed previously under rheumatic heart disease.

2.7.5 Recommendations

Primary emphasis should be in the following areas:

1. Utilize currently available methods to diagnose, prevent, and treat streptococcal infection, and thus prevent initial and recurrent episodes of rheumatic fever.
2. Utilize currently available methods to diagnose, prevent and treat infective endocarditis.
3. Generate new knowledge about the biologic properties of the streptococcus and the host's immunologic reactions to this organism for application regarding:
 - More rapid, accurate, and inexpensive methods to diagnose streptococcal infection
 - Development of more effective antistreptococcal antibiotics
 - Development of antistreptococcal vaccine.
4. Develop and evaluate noninvasive methods to assess cardiac function in children and adults, and relate the results of cardiac function testing to physical activity and work recommendations, to recommendations for surgical intervention, and to determination of long-term prognosis.
5. Identify risk factors for the development and recurrence of rheumatic fever--both host and organism (streptococcal) factors.
6. Evaluate the behavioral and motivational factors in patient compliance with recommended medical care, as patient education regarding health care and prevention of recurrent disease is a major factor in rehabilitation. Evaluate efficacy of patient and public education programs in influencing these factors.



7. Elucidate the "natural history" of surgically treated chronic rheumatic heart disease with emphasis on restoration of function and on reduction of morbidity and mortality. The data on functional capacity is needed for rehabilitation efforts which include counselling regarding career or job choice and possible retraining, concerns regarding employability, insurability, etc.
8. Identify the etiologies and incidence of nonrheumatic valvular disease.
9. Identify the incidence and types of cardiovascular complications of drug abuse. Disseminate information to the public regarding the cardiovascular complications of drug abuse and provide professional education regarding their occurrence, diagnosis and management.



2.8 CARDIOMYOPATHY

2.8.1 Introduction

Cardiomyopathy, a disease which primarily affects the heart muscles, results in dysfunction of the heart. The clinical presentation includes cardiac enlargement, congestive heart failure, arrhythmias, embolic phenomena, electrocardiographic abnormalities, and occasionally sudden death.

Cardiomyopathy is a chronic incapacitating disease which occurs in both adults and children. Multiple and possible interacting etiologic factors are responsible; however, most frequently, the cause is unknown. Identification of the etiology(ies) and pathogenesis is required for all efforts directed toward prevention, diagnosis and treatment of cardiomyopathy.

The clinician must learn to suspect and recognize cardiomyopathy, to identify the subgroups, and to develop a systematic approach to elucidate the cause. He must be aware of the common complications and be able to institute treatment to retard or prevent them.

2.8.2 Scope

While little or no information is available regarding the incidence, prevalence, or geographic distribution of cardiomyopathy, it is known to be common in the United States. Some estimates show that alcoholic cardiomyopathy alone exceeds congenital heart disease as a cause of morbidity.

The lack of information about cardiomyopathy is due partly to the lack of specific diagnostic criteria or other identifying laboratory tests.

Current therapy is symptomatic and generally unsatisfactory; the prognosis is grave after the onset of congestive heart failure. Pharmacologic and surgical therapy have appeared promising only in the obstructive variety of cardiomyopathy. Elucidation of the pathogenesis may aid in developing specific therapeutic measures.

2.8.3 Summary of Approaches

Determination of Etiology(ies) and Mechanism(s) of Myocardial Damage in Cardiomyopathy

The fundamental defect or abnormality in cardiomyopathy is not well understood; routine examination of the gross and microscopic structure of the heart does not reveal sufficient abnormalities to explain the severe pump failure. Emphasis must clearly be placed on defining the etiology(ies) and pathogenesis of cardiomyopathy and on characterizing the myocardial abnormalities.

Defects in myocardial cellular energy production or in the process of excitation-contraction coupling must be elucidated. Cellular and subcellular, biochemical and immunologic alterations must be investigated.

Epidemiologic studies for characterization and classification of naturally occurring cardiomyopathy in man, and development and utilization of artificial and naturally occurring animal

models of human cardiomyopathy, will enable evaluation of the role(s) of and diagnostic criteria for cardiomyopathy due to: alcohol; malnutrition (including obesity); infection, particularly viral; the peripartal state; physical (radiation, thermal, etc.) stress; genetic and immune factors; age; endocrine abnormalities (particularly thyroid, catecholamine, diabetes); and drugs. Animal models are of particular value for investigations not ethically possible in man.

Identification is required of conduction system abnormalities related to arrhythmias and sudden death, of factors responsible for the high incidence of thromboembolic complications, of the relationship to pericardial disease, and of abnormalities outside the heart (e.g., abnormalities of skeletal muscle or of peripheral blood) which might prove of diagnostic value in cardiomyopathy.

These approaches are dependent upon development of new equipment and techniques and upon the training of research personnel, physicians and scientists.

Identification of Risk Factors Predisposing to Cardiomyopathy

Identification of factors which may affect susceptibility to cardiomyopathy is needed, as they may identify susceptible populations for preventive and therapeutic efforts.

Animal models can be used to test clinically suggested risk factors, viruses, alcohol, malnutrition, pregnancy or peripartal state, genetic factors, immune factors, hypoxia, physical activity, stress, crowding, toxins, etc.



Evaluation of Functional Impairment in Cardiomyopathy

More accurate and sophisticated noninvasive methods must be developed for the early detection and quantification of myocardial dysfunction (anatomic, physiologic, clinical). Longitudinal studies using these noninvasive indices of myocardial function will provide a better description of the natural history of cardiomyopathy, identification of more subtle forms of cardiomyopathy with an increased possibility of reversibility, assessment of environmental factors which retard or accelerate cardiomyopathy, and the effect of therapeutic intervention and rehabilitation efforts on cardiomyopathy.

The development of a safe cardiac biopsy instrument will enable function-structure correlations.

Improvement of Management of Patients with Cardiomyopathy

Development of educational materials and programs for physicians, health care personnel, and patients regarding newly acquired information about the diagnosis and therapy of cardiomyopathy; establishment of and expansion of laboratories, with developments of new procedures to rapidly and reliably test for myocardial infection, toxicity, environmental hazards, etc.; and identification and dissemination of information regarding drugs which may produce myocardial damage in man will help improve the delivery of care to patients with cardiomyopathy. The therapy of cardiomyopathies is presently palliative and symptomatic, i.e., management of the congestive heart failure with digitalis, diuretics, and



sodium restriction. Optimal therapy, management and rehabilitation of patients requires controlled evaluation and establishment of specific indications for controversial therapeutic modalities currently in use: bedrest of varying duration, antiinflammatory and immunosuppressive agents, anticoagulant therapy, prophylactic antiarrhythmic drugs, pacemakers, and surgery.

Newly developed modes of therapy which become available as the disease pathogenesis is better understood must be similarly evaluated in controlled clinical trials--viral vaccines, antithrombotic agents, protein or other nutrient supplementation, antiarrhythmic drugs, partial or temporary cardiac bypass, and cardiac transplantation or artificial heart development.

In a well-defined and increasingly recognized clinical subgroup, idiopathic hypertrophic subaortic stenosis, comparative evaluation of pharmacologic modes of intervention and indications for medical versus surgical therapy must be established.

Potentially cardiotoxic drugs are currently used to treat the complications of cardiomyopathy. Improved drug development should be directed toward availability of antiarrhythmic agents without negative inotropic effect, positive inotropic agents without arrhythmogenesis, diuretic agents without cardiotoxicity, and contraceptive agents without thrombogenic properties.

2.3.4 Recommendations

Research in cardiomyopathy should focus on the following areas:

1. Identify etiologies of cardiomyopathy by epidemiologic methods, viral and immunologic research, and development and utilization of animal models.
2. Determine the mechanisms of myocardial damage by application of biochemical, biophysiological, physical, and pharmacologic techniques.
3. Identify risk factors predisposing individuals to cardiomyopathy, such as viruses, alcohol, pregnancy, age, malnutrition, stress, immunologic factors, genetic factors, etc.
4. Develop noninvasive techniques to assess myocardial function to aid in the early identification of cardiomyopathy, to delineate the natural history of the disease, and to evaluate therapeutic and rehabilitative intervention.
5. Train physicians to recognize, to systematically identify or classify, and to appropriately treat patients with cardiomyopathy.
6. Develop better (noncardiotoxic) drugs to treat manifestations of cardiomyopathy. Evaluate current controversial therapeutic approaches, i.e., bedrest, corticosteroid hormones, immunosuppressive agents, etc.
7. Characterize idiopathic hypertrophic subaortic stenosis, a specific form of cardiomyopathy, as to incidence, natural history, etc., to enable evaluation of medical and surgical therapy.

2.9.1 Scope of the Problem

An arrhythmia is an alteration in the normal initiation and propagation of the cardiac impulse. It is not a 'disease but a manifestation of most major cardiac diseases considered in this Panel report. Arrhythmias, together with cardiac failure, constitute final common pathways of heart disease which the physician is called upon to prevent or treat. More than half the victims of coronary heart disease die of arrhythmia, many suddenly without warning and without opportunity for therapeutic intervention. Arrhythmias are also a major cause of morbidity in rheumatic heart disease. The development of tools necessary for the effective prevention and treatment of arrhythmias is dependent upon understanding many aspects of the normal generation and propagation of the cardiac impulse. Research must extend from molecular and cellular studies through the examination of individual affected patients to large-scale epidemiologic investigations. The major impact which medicine has had on mortality from coronary artery disease has been in the recognition, prevention, and treatment of arrhythmias occurring during the early hospital period of acute myocardial infarction. It is now recognized that most fatal arrhythmias occur before admission to the hospital. How to prevent or treat these major, often fatal, events typifies the challenge faced by this area.



2.9.2 Summary of Approaches

Problems related to arrhythmias may be conveniently considered in four areas:

- Ventricular arrhythmias and fibrillation
- Ventricular asystole
- Atrial arrhythmias
- Crib death.

Ventricular Arrhythmias and Fibrillation

Ventricular arrhythmias are the most serious rhythm disturbances in patients with heart disease. Most ventricular arrhythmias are unstable and portend the appearance of ventricular fibrillation, a disorganization of impulse propagation in the ventricle which results in lack of effective mechanical contraction and consequently a failure of cardiac output and death. Since ventricular fibrillation is usually a fatal event, it is first necessary to define retrospectively the characteristics of afflicted individuals. Studies are needed which follow reasonable population samples systematically in a prospective study. This is a long-term research effort which is not likely to yield complete results for 8 to 10 years. In the meantime, it would be desirable to focus on the identification of predisposed or susceptible individuals. At present, no method exists for predicting the individual at risk from ventricular fibrillation. Such questions as to whether or not electrical instability antedates the development of ventricular fibrillation must be answered.

Susceptible individuals, such as patients who have recovered from myocardial infarction, can be studied with exercise stress testing, electrical pacing of the heart, or the application of certain psychological tests. It may thus be possible to define a subpopulation at high risk which can be studied more effectively with respect to preventive and therapeutic measures. The necessary corollary of these studies is the development of improved methods for the continuous detection and recording of cardiac arrhythmias.

An approach to the prophylaxis of arrhythmias in high-risk groups is the administration of suitable drugs to prevent the onset of ventricular arrhythmias and fibrillation. Drugs presently available are of limited efficacy and are characterized by excessive side effects. An intensive search is required to develop better drugs for long-term prophylactic use. The most promising approach is likely to derive from better understanding of structure activity relationships in antiarrhythmic drugs so that drugs of desired characteristics could be synthesized in a planned fashion. In order to facilitate this approach, a more reliable cellular or animal model for the testing of prophylactic arrhythmia drugs would be desirable. Subsequent clinical testing of susceptible populations requires the development of instruments for effective, convenient monitoring of ambulatory individuals over long periods of time, as well as reduction of the data obtained from such devices without excessive time investment by highly trained individuals. When suitable drugs are available, a study could be devised to determine whether it is possible to reduce prehospital mortality from arrhythmias.

Factors meriting attention in the development of rational prophylactic measures include the function of the autonomic nervous system, the effect of drugs and other potentially toxic agents, the role of genetic factors, contribution by systemic illnesses, and the state of coronary perfusion. The exact mechanism by which impairment of myocardial perfusion precipitates clinical arrhythmias remains unknown. Diminished oxygen tension alone does not seem responsible and it would appear that attacking this most important problem requires not only the development of satisfactory animal models for human coronary disease but also development of instrumentation for the precise localization of arrhythmia foci in the heart. Understanding the effect of ischemia on the function of the cell and its excitable membrane seems necessary to answer this problem. Other major etiologic causes of ventricular arrhythmias include cardiomyopathy, aortic stenosis, certain diseases of the mitral valve, and infiltrative diseases of the myocardium. Structural studies of the heart likely to yield answers include detailed examination of the coronary circulation with respect to tissues responsible for excitation and conduction and detailed examination of the innervation of the heart and its role in ventricular arrhythmias. The mechanism of ventricular fibrillation must be examined at its cellular, suborgan, and organ level. As a corollary, the determination of the molecular mechanism of maintenance of cell membrane potential and detailed delineation of the biochemical pathways of membrane function would be most desirable.

Better electrical devices as well as drugs are required to revert ventricular arrhythmias to normal sinus rhythm. There is a special need to plan to deal with ventricular arrhythmias

and fibrillation within the framework of emergency medical services and general health care delivery. Major emphasis must be given to education and training of health care personnel, as well as policemen, firemen, and other individuals in high-risk occupations in techniques of resuscitation, particular attention being given to recognition and emergency treatment of ventricular arrhythmias.

Ventricular Asystole

Asystole is the cessation of electrical and, consequently, mechanical action of the heart. While the majority of sudden deaths appear related to ventricular fibrillation, little information is available concerning the fraction of patients dying suddenly of asystole. A population at risk for asystole should be identified not only by monitoring, but also by basic methods such as His's bundle recording, atrial pacing and drug challenges to elucidate predictors of subsequent asystole. As discussed previously, the delineation of mechanisms and cause of asystole involves application of a variety of methods of investigation including examination of the conduction tissue and elucidation of the mechanism of impulse generation and propagation at a cellular and molecular level. There is need for monitoring instruments and data reduction devices similar to those required for the study of ventricular fibrillation. Electrical pacemakers are currently useful in the treatment of asystole and restoration of an effective cardiac rhythm. These devices can be substantially improved, both with respect to longevity of energy sources and reduction in size. Research should also be directed to develop improved drugs for the prevention or treatment of asystole.



Atrial Arrhythmias

Abnormalities in the atrial rhythm do not have as serious and immediately grave prognoses as do ventricular arrhythmias or asystole. However, they contribute substantially to long-term morbidity and mortality. A search is required to determine the mechanism of atrial fibrillation and other atrial arrhythmias and to develop improved techniques for detection and diagnosis. The reason for association of atrial fibrillation with certain diseases is largely unexplained. Insight must also be gained from study of patients with the "sick sinus" syndrome. It will be necessary to study in detail the activity of the sinus node itself and the propagation of the impulse between the sinus node and atrium. In patients with the Wolff-Parkinson-White syndrome, precise anatomic localization of the bypass tract is needed so that effective and safe surgical procedures may be undertaken.

At present, reliable drugs for maintaining sinus rhythm or for reversing atrial fibrillation are not available. New drugs and improved electrical pacing techniques for maintaining sinus rhythm in patients with severe or recurrent atrial arrhythmias are also desirable.

Crib Death

Crib death is a form of sudden death in the paranatal period which may or may not be related to cardiac arrhythmia. Although approximately 10,000 crib deaths occur annually, the etiology of this syndrome is not understood. Pathologic studies have not been revealing. Considerable investigation



is required to determine the etiology of crib death in order that an approach to prevention can be developed. The most promising avenues for investigation include an examination of the epidemiology and pathophysiology of this syndrome, as well as determination of whether atrioventricular or intraventricular conduction is abnormal in susceptible infants.

2.9.3 Recommendations

Research on arrhythmias should focus on these goals:

1. Determine the mechanism of generation of cardiac arrhythmias through understanding the normal initiation and propagation of the cardiac impulse and how it is altered in various disease states. This will permit an understanding of how ischemia leads to fatal arrhythmias and allow for the rational design of drugs for the effective prophylaxis and treatment of arrhythmias.
2. Determine specific structural and functional abnormalities of the heart responsible for atrial and ventricular arrhythmias and for heart block.
3. Identify individuals or groups prone to ventricular fibrillation or asystole through epidemiologic studies and provocative tests. This will serve to attack directly the problem of sudden death by identifying the population at risk.
4. Determine whether or not prophylaxis can reduce the incidence of death from cardiac arrhythmias, utilizing either drugs or electronic devices. Selected groups of individuals at risk should be treated with available agents or those to be developed through research to determine whether or not sudden death can be prevented.
5. Develop new drugs for the treatment of arrhythmias and methods to test them through subcellular, cellular and animal models, and finally in human studies. It is important to devise a rational approach to drug development and design through an understanding of the relationship of chemical structure of a drug to its action as an antiarrhythmic agent.

6. Develop improved bioengineering devices for diagnosis and treatment of arrhythmias. Of particular importance are improved monitoring systems for ambulatory detection of arrhythmias, automatic analysis of the output of these devices, longer-lived and more compact pacemakers, and new devices to treat ventricular fibrillation.
7. Educate the public in the recognition and initial management of the life-threatening emergency caused by a sudden arrhythmia.



2.10 CARDIAC FAILURE

2.10.1 Introduction

Cardiac failure, together with arrhythmias as discussed previously, represents a major cause of death and may be the end result of any cardiac disease. Cardiac failure occurs when the heart has been sufficiently damaged by malfunction of cardiac muscle, cardiac valves, or other essential structures so that its ability to pump blood is insufficient to empty the venous system and to meet the needs of the body.

2.10.2 Scope of Problem

At least one-and-a-half to two million Americans suffer from chronic cardiac failure. There are approximately 250,000 new cases each year, one-quarter to one-third of whom are under 65 years. Cardiac failure is a major cause of death. In hospital costs alone cardiac failure accounts for 300,000 to 600,000 hospital admissions annually, representing a total cost for hospitalization of more than one-half billion dollars annually. In its chronic form, cardiac failure can persist for decades, preventing gainful employment or normal living, leading to protracted suffering, while incurring progressively increasing medical expense.

The prevention of heart failure must involve an attack on the etiologic disease processes: hypertension, valvular stenosis and regurgitation, coronary disease, and other causes discussed in this Panel report. Effective treatment of heart failure, however, usually involves not only treatment of the

underlying disease process, but also of the state of failure itself. At present, this latter treatment is primitive and empirical, largely because the fundamental disturbance of heart muscle which we identify as cardiac failure is not understood. Consequently, the major emphasis of this section is to gain detailed understanding of the pathophysiology of cardiac failure on a molecular, cellular, and organ basis.

2.10.3 Summary of Approaches

Diagnosis and Evaluation of Cardiac Failure

Presently, the only clinical clue to left heart failure prior to the appearance of overt pulmonary congestion is a diminished exercise tolerance or the subjective sensation of dyspnea as reported by the patient. Invasive techniques can demonstrate an elevated end-diastolic pressure, but they have limited application. Noninvasive methods must be improved to permit precise evaluation of cardiac function and early detection of impending heart failure.

The Pathophysiology of Heart Failure

Investigation of the function of the heart should be continued to answer questions concerning coronary circulation, cardiac failure, alterations in innervation, regional abnormalities of ventricular function, the lymphatic circulation, the impact of disordered rhythm, and the role of abnormalities of the cardiac skeleton in heart failure. The neural and humoral control of cardiac function, both at an organ and a

cellular level, as it relates to cardiac failure is an important area for investigation. Because myocardial hypertrophy generally accompanies cardiac failure, the mechanism of initiation and maintenance of hypertrophy, the control of new vessel and connective tissue growth, the turnover of cellular components, and the proliferative capacity of heart muscle cells require better definition. Attempts should be made to provide a basis for future efforts to allow controlled regeneration of heart muscle. A major consequence of cardiac failure is alteration in the distribution of body fluid volume. Therefore, the role of the renin-angiotensin-aldosterone system, factors responsible for sodium retention by the kidney, and the contribution of other humoral factors, such as anti-diuretic hormone, must be explored.

Derangements in reflex control mechanisms of fluid volume shifts and sodium retention also should be examined in cardiac failure. Alterations in the peripheral circulation that lead to abnormal distribution in blood flow to various organs must be examined and the effects of cardiac failure on the microcirculation and organ nutrition and function must be defined. The mechanism of these alterations in initiating interstitial edema must be better understood.

Interrelationships between the heart and lung in cardiac failure, including the effects of arterial hypoxemia, alterations in pulmonary vascular control, altered blood flow distribution within the lungs, pulmonary hypertension and the effects of exudation of fluid in the alveoli and in the pleural space have to be determined.



fundamental to the study of cardiac failure is an understanding of the disordered contraction of the cardiac cell. How are energy production, excitation-contraction coupling, and contraction disturbed in cardiac failure? What are the compensatory alterations in cellular control mechanisms? With respect to the function of affected organs, how does reduced blood flow affect metabolic and transport functions in the liver, the kidney, the blood, etc.?

Therapy of Heart Failure

The cornerstones of therapy of heart failure are the cardiac glycosides, a class of drugs used widely since the early 18th century. These drugs are not ideal as they may have serious, sometimes lethal, side effects. They were first used on an empirical basis and only recently has insight been obtained into their mechanism of action. Fundamental questions to be answered relate to the mechanism of their useful inotropic effects and their undesirable arrhythmogenic effects. Do these have identical mechanisms or are they separable? The digitalis glycosides have the smallest therapeutic to toxic ratio of all cardiac drugs, so separation of inotropic and arrhythmogenic effects would significantly improve patient care. As a corollary, better methods for reversing and treating digitalis toxicity must be found. The mechanism for altered sensitivity to the cardiac glycosides, present in a variety of abnormal physiologic states and disease processes, needs better definition as does the interaction of cardiac glycosides with other drugs. Cardiac glycosides have extracardiac effects, and their importance with respect to either therapy or toxicity requires better definition. While cardiac glycosides are accepted in the treatment of cardiac

failure, their "prophylactic" usefulness in patients with heart disease prior to the advent of overt cardiac failure needs further examination. Other inotropic drugs, such as catecholamines or their derivatives, are extremely powerful inotropic agents, but can be used only transiently to treat cardiac failure. Better understanding of these drug actions may lead to development of new classes of drugs equivalent to the cardiac glycosides in their inotropic effect but with fewer toxic side effects. The possibility that drugs that altered impedance to ventricular ejection would facilitate the treatment of left ventricular failure needs further exploration as do therapeutic modalities which alter cardiac filling pressure.

A second major approach to the treatment of cardiac failure entails induction of diuresis. Many effective diuretic agents are now available and data as to their cellular mechanism of action are rapidly being acquired. Further knowledge is needed of the effects of diuretics on renal cellular function and intrarenal hemodynamics. The definition of the relationship of these drug actions to the tubular actions of extrarenal hormones gives considerable promise of better patient care. The extrarenal effects of diuretic agents, e.g. on cardiac function, vascular resistance, and release of circulating hormones, need exploration. While much progress has been made in the development of a wide variety of diuretic agents, new drugs, especially vasopressin antagonists, would be desirable.

Therapy directed at altered ventilatory function is needed in the treatment of acute left ventricular failure. Temporary assistance devices replacing the function of the heart



or lungs have been employed in extreme cardiac failure, but these need further development before they become generally applicable treatment modalities. Irreversible cardiac failure requires consideration of cardiac transplantation or mechanical cardiac replacement as discussed in prior sections.

Optimal care of cardiac failure is complex; continuing physician education is needed to ensure optimal patient care. Enhanced public education in early recognition of symptoms of congestive heart failure as well as education of physician's assistants to perform routine care for this common major problem would be of value.

2.10.4 Summary

Heart failure is a common cause of morbidity and mortality because it complicates most cardiac diseases. The reasons why the heart fails are complex and incompletely understood so therapeutic efforts generally involve either the use of traditional empirical agents which increase the force of contraction of the heart, such as the digitalis glycosides, or newer remedies aimed at reversing the manifestations of heart failure, such as diuretics. Much effort must be expended to gain understanding of the pathophysiology of cardiac failure needed for the rational development of new therapeutic modalities.

2.10.5 Recommendations

1. Devise improved methods for the detection, quantification and etiologic diagnosis of cardiac failure in man, both at clinical and cellular levels.

2. Determine the basis, significance and potential reversibility of alterations in cardiac function and abnormalities in cardiac cell growth which accompany heart failure by examining cellular and molecular abnormalities in the hypertrophied and failing heart.
3. Characterize neural, humoral and cellular factors controlling cardiac hemodynamics, the peripheral circulation and body fluid volume, composition and distribution in man. Determine abnormalities in these systems and in organs other than the heart that occur in cardiac failure.
4. Devise better therapy for cardiac failure, utilizing the knowledge being developed under recommendations (1) through (3) to extend our ability to utilize existing and to develop new pharmacologic agents.
5. Improve the delivery of care of cardiac failure both by providing more effective therapeutic approaches (above) and through continuing education of physicians and health care personnel, particularly regarding objective assessment of cardiac function and correlation of this with recommendations for activity and for work.
6. Increase the number of trained investigators capable of achieving these significant research goals in the field of cardiac failure.
7. Find better animal models for cardiac failure utilizing both spontaneously occurring animal disease and various induced forms of this condition.



Shock is a state characterized by inability of the heart and/or the peripheral circulation to maintain an adequate arterial blood pressure and organ perfusion. If untreated, it rapidly leads to irreversible damage to organs and death of the patient. Shock should be regarded as a secondary phenomenon. It is a frequent and often fatal complication of many disorders including acute myocardial infarction, trauma, hemorrhage unrelated to trauma, infection and burns. Shock also occasionally complicates medical and surgical therapy. Shock is still the leading cause of death in patients who have come under the supervision of the medical care system following myocardial infarction. Shock, secondary to trauma, is the leading cause of death in U.S. citizens under the age of 45. Shock could be eliminated as a major cause of death if the primary illnesses which cause it could be eliminated, but the likelihood of eliminating coronary heart disease and trauma in the foreseeable future is slight. Consequently, substantial effort is justified to understand the pathogenic mechanisms of shock and to improve its treatment. This effort should include more widespread application of existing knowledge, the earlier application of forms of treatment known to be beneficial, the critical evaluation of promising new forms of treatment and the acquisition of new knowledge to solve important unanswered questions.

2.11.2 Summary of Approaches

Better Understanding of the Pathophysiology of Shock

Inadequate tissue perfusion is a common feature of shock regardless of the insult which initiates it. Consequently, approaches to understanding the shock state must focus on the characterization of the mechanisms and consequences of hypoperfusion. Studies should evaluate the function of the microcirculation in shock, particularly with respect to the control and distribution of flow and its influence on tissue metabolism, the control of perfusion at capillary level, and the regulation of the distribution of flow in the microcirculation. Of particular importance is understanding the mechanisms which contribute to loss of control of capillary fluid balance.

Oliguria and anuria are common consequences of shock. Better models to study acute renal failure in primates are needed, so that the mechanisms of anuria can be studied and its prevention and treatment evaluated. In addition to kidney damage, lung function deteriorates following prolonged periods of hypoperfusion. Elucidation of the factors which contribute to these pulmonary changes is needed. Is there impairment of intravascular perfusion or the development of an abnormality of fluid and protein exchange across the alveolar capillary membrane? Decrease in hepatic blood flow may be a major factor contributing to the lethal outcome of shock induced by hemorrhage or endotoxin. Hypoperfusion of the small intestine and pancreas has also been implicated. Studies are needed to characterize the distribution of flow to visceral organs; and a resolution of the question of

whether organ failure or release into the circulation of humoral factors from hypoperfused organs is a major factor in the outcome of the shock state.

The heart plays a central role in the etiology of cardiogenic shock and an important role in the end states of several other forms of shock. Cardiac output and distribution of cardiac output to various organs have to be characterized in the various forms of shock. Coronary blood flow, the metabolism and mechanics of ischemic muscle and the electrophysiological basis of arrhythmias are poorly understood in various forms of shock.

Preliminary studies indicate that alterations of the clotting and fibrinolytic systems are common in shock. The incidence of these abnormalities and their significance, as well as potential for treatment, needs attention. Changes in the autonomic nervous system and the role of these changes in the control of distribution of blood flow in shock must be clarified. The potentially detrimental effect of peripheral vasoconstriction and enhanced beta-adrenergic stimulation to the heart in some forms of shock must be clarified and the effect of appropriate intervention evaluated. Detrimental effects on blood pressure or organ perfusion by released lysosomal enzymes, endotoxin, reticuloendothelial depressant substances and other materials circulating in abnormal levels in the shock state must be quantified and their physiologic significance documented.

Treatment of Shock

While treatment of all forms of shock is unsatisfactory, the treatment of cardiogenic shock is particularly unrewarding, since there has been little influence on the greater than 90 percent mortality even with all current therapeutic modalities. Much could potentially be gained from early therapy so investigations seem indicated to define the subset of patients at high risk of developing irreversible cardiogenic shock. Efforts must be focused on implementation and evaluation of modern methods of transportation and of early detection and treatment of shock. Objective studies of the following treatment modalities are recommended: The effect of inotropic agents including digitalis, isoproterenol, glucagon, and dopamine; the role and consequences of vasoconstrictor therapy; the value of drugs causing vasodilation; the value of alpha adrenergic blockade, and the effect and benefits of temporary circulatory assistance.

Clearly drug distribution and disposition is altered in cardiogenic shock. This must be quantified before effective dose regimens can be outlined. The kidney plays a central role in shock and effects of treatment designed to preserve renal function must be evaluated. Better methods, including noninvasive techniques to quantify the shock state involve improved measurement of venous pressure, left ventricular pressure and function, intravascular volume and the distribution of cardiac output. Better volume expanders must be developed and the potential pharmacologic action of these volume expanders, as well as of existing ones, must be documented. The best forms of prevention and treatment of



shock lung must be sought, as well as the role of relief of intravascular obstruction, superimposed infection, and oxygen toxicity. Objective evaluation of existing techniques and the development of new devices for circulatory assistance would be of great value.

An attack on the problem of cardiogenic shock involves cooperation between individuals trained in basic science, pharmacology, medicine, surgery, and epidemiology. Effective bridges must be built between traditional disciplines, and individuals must be trained who can effect these interdisciplinary collaborations. Effective evaluation of the treatment of shock will require collaborative studies and the pooling of data with modern methods of information retrieval.

2.11.3 Summary

Shock is the consequence of many catastrophic derangements of the cardiovascular system. Its prevention involves prevention of the primary disease process causing it. Since this is not yet feasible in most instances, substantial energy must be devoted to understanding the pathophysiology of cardiogenic shock, as well as to improving treatment modalities as a result of such enhanced knowledge.

2.11.4 Recommendations

1. Develop a more complete and integrated understanding of the pathophysiological changes and their sequence of development in various forms of shock.
2. Determine the nature and sequence of changes in specific organ functions caused by hypoperfusion.

3. Systematically evaluate the distribution and effects of drugs currently used in the treatment of shock.
4. Develop better models of shock in experimental animals which satisfactorily mimic the human condition. These are essential to recommendations (1) through (3).
5. More widely apply existing methods of hemodynamic and metabolic assessment to treatment and evaluation of patients with shock.
6. Develop and evaluate noninvasive techniques such as ultrasound and isotope studies to evaluate the critical variables in patients with shock and to follow the changes consequent to therapy.
7. Further evaluate available and new devices to assist the circulation and their role in various forms of shock.
8. Determine whether earlier application of available or new forms of treatment will reduce the mortality from shock.
9. Support the training of basic investigators and teams of clinical investigators who will conduct the above studies.
10. Encourage collaborative studies and detailed registries of patients with common forms of shock.



PART III

SUMMARY OF PANEL RECOMMENDATIONS





PART III
SUMMARY OF PANEL RECOMMENDATIONS

In this section the Panel has listed in summary form major recommendations for new or broadened programs; in many instances, these represent a synthesis of recommendations which have arisen from several Task Groups. These summary recommendations have been ordered under four headings, but these should not be considered to represent priority. The Panel strongly urges a balanced approach with equal emphasis on approaches in all four categories. It would be an error to emphasize one to the exclusion of others.

The approaches are presented under the following four headings:

- Acquisition of new knowledge through research
- Measures which will facilitate the development, evaluation and early application of new techniques for prevention, diagnosis, treatment and rehabilitation

- Evaluation of existing forms of therapy
- Immediate application of currently available knowledge for the prevention, diagnosis, treatment and rehabilitation of patients.

Every Task Group emphasized the acquisition of new information as essential to the solution of its assigned problem. This is especially true for the major disease processes such as atherosclerosis and hypertension, and also in regard to the manifestations such as arrhythmias and congestive failure. Accordingly, fundamental studies of pathogenesis and mechanisms of these diseases and their common sequelae are of high priority.

Acquisition of new knowledge is needed in the field of atherosclerosis since we do not understand many critical steps in the process by which arteries are narrowed and occluded. We cannot design effective programs to prevent coronary and peripheral vascular disease until these steps are clearly defined. The cause of hypertension will not be understood and its definitive cure will not be devised until the specific derangement in cardiovascular homeostasis which it represents is understood. The effective cure of hypertension will diminish the incidence of stroke. The prevention of sudden death due to arrhythmias cannot be accomplished until the effects of ischemia on the initiation and propagation of the cardiac impulse are understood. The optimal treatment of heart failure and the prevention and treatment of cardiomyopathy will not be available until the nature of the derangement of cardiac cell function with respect to excitation-contraction coupling, the contractile process and their regulation are understood. The incidence of congenital heart disease will be minimized only when all the etiologic, viral, drug and genetic factors are identified.



The implementation of these goals requires both physical and human resources. Laboratories alone are not sufficient if they are not staffed by trained individuals at many levels of competence. The acquisition of new knowledge requires a pool of trained scientists with competence to tackle a wide variety of problems relevant to cardiovascular disease. Epidemiologists, clinical investigators, pharmacologists, pathologists, physiologists, biochemists, and biomedical engineers are all needed. Creative young people must be attracted to cardiovascular research both at a graduate level and at a postgraduate level. Following training, mechanisms must be established for the stable support of young scientists to continue investigative work. In addition to scientists and physicians, the implementation of many of these programs requires other health professionals such as nurses, dieticians, technologists, physical therapists and health educators and counselors.

3.1.1 Atherosclerosis

Prevention of atherosclerosis will contribute directly and in a major way to prevention of coronary heart disease and peripheral vascular disease, and to a lesser extent to the prevention of stroke. The development of more effective methods for the prevention of atherosclerosis depends on better understanding of the mechanisms by which the genetic and environmental factors exert their action. The search for etiologic agents and risk factors in diet, behavior, psychosocial stress and other features of the geochemical environment is likely to provide leads for new preventive regimens. Continued and intensified research efforts in cell biology, lipoprotein structure, enzymes controlling cholesterol



metabolism, interactions of macromolecules in the arterial wall, and other basic pathogenetic mechanisms will provide a rational basis for all methods of prevention.

3.1.2 Coronary Heart Disease

Specific factors that precipitate acute myocardial infarction and ischemia are only generally but not specifically understood. Detailed investigation of these precipitating factors is needed. A better understanding of factors influencing coronary blood flow and changes in myocardial metabolism which occur during ischemia is needed to provide a more rational basis for the treatment of coronary heart disease. Methods of preservation of myocardial function and viability in the face of ischemia must be explored.

3.1.3 Hypertension

The determination of the etiology of hypertension and its effective treatment or prevention bears upon the prevention of stroke, cardiac failure, cardiac arrhythmias, cardiac deaths, accelerated atherosclerosis and renal failure. The fundamental cause of hypertension must be defined through an examination of the function of the kidney, the central and autonomic nervous system, abnormal distribution of body fluid volumes, the pathophysiology of vascular smooth muscle, and the effects of circulating hormones and possible altered receptor sensitivity. Knowledge of the roles of specific environmental agents, dietary factors such as salt, obesity, and psychosocial factors are essential to designing preventive regimens.



3.1.4 Stroke and Peripheral Vascular Disease

The specific effects on cellular and organ function of tissue ischemia need to be defined so that appropriate measures can be taken in the event of an arterial occlusion to limit the extent of ischemic injury and to allow sufficient time for revascularization procedures. This applies equally to stroke, myocardial infarction and peripheral vascular disease.

3.1.5 Congenital Heart Disease

The etiology of congenital heart disease must be elucidated with respect to genetic traits, viral agents, and teratogenic factors in order to develop specific methods for prevention. Basic mechanisms of normal and abnormal cardiovascular function in the fetus and neonate must be investigated to provide safer and more effective procedures for diagnosis and therapy.

3.1.6 Rheumatic Fever

Generation of new knowledge about the biologic properties of the streptococcus and the characteristics of the immunologic response of individuals who develop rheumatic fever is a necessary prerequisite for more rapid, accurate, and inexpensive methods for diagnosis of streptococcal infection. Such information is also essential for the development of more effective antistreptococcal antibiotics, and the development of antistreptococcal vaccines. Knowledge of host and streptococcal factors which determine susceptibility may facilitate the identification of individuals at high risk and lead to more effective intervention against rheumatic fever.



3.1.7 Cardiomyopathy

It is in this disease area that the acquisition of new knowledge is most urgently needed. A wide variety of etiological processes appear to be capable of resulting in cardiomyopathy. The interaction of genetic and environmental factors is responsible in some patients. Viral infections are also important. Better techniques for identification of viral infection would undoubtedly enable a better understanding of the disease in some patients. Improved techniques for the biochemical, anatomical and physiological study of diseased heart muscle will be important.

3.1.8 Arrhythmias

The mechanism of generation of cardiac arrhythmias must be elucidated by understanding the normal initiation and propagation of the cardiac impulse and determining how this is altered by ischemia and other disease processes which result in disturbances of cardiac rhythm.

3.1.9 Cardiac Failure

The cellular abnormalities occurring in congestive heart failure, cardiac hypertrophy and cardiomyopathy must be examined from a biochemical, physiologic, biophysical, and pharmacologic point of view to bring about improved understanding of these disease processes.

Aspects of cardiac cell function to be examined include studies of excitation-contraction coupling, contraction, and control of contraction. The role of the autonomic nervous



system, circulating humoral agents and their receptors must be defined. The difference between abnormal cardiac hypertrophy and normal cardiac growth and regeneration must be understood. Since the primary manifestation of heart failure is an alteration in the compartmental distribution of body fluid, the effects of heart failure and their optimal treatment will be better understood through an examination of factors controlling volume, composition, and the distribution of body fluid.

3.1.10 Shock

Better understanding of the pathophysiologic changes in shock and cardiac failure must be pursued, with particular attention to damage to specific organs such as the kidney, lung, and visceral organs.



3.2 MEASURES WHICH WILL FACILITATE THE DEVELOPMENT, EVALUATION AND EARLY APPLICATION OF NEW TECHNIQUES FOR PREVENTION, DIAGNOSIS, TREATMENT AND REHABILITATION

The Panel considers that methods and resources which will facilitate the development, evaluation and early application of new and improved techniques of diagnosis, prevention and treatment are essential.

3.2.1 Therapeutic Agents

The current system of new drug development and evaluation needs improvement. Drugs are available elsewhere in the world which might prove useful in the treatment of hypertension but are not yet available for trial in the United States. Attention should be given to developing a system whereby drug testing and approval can be more readily and effectively obtained without sacrificing the important safety procedures inherent in the current review process. New drugs are needed in the treatment of hyperlipidemia, intravascular thrombosis, hypertension, the prophylaxis and treatment of arrhythmias, and the therapy of cardiomyopathies and cardiac failure. It is recommended that a facility for the formulation, synthesis, and distribution of new drugs (including a central clearing-house for new drug information) be established.

3.2.2 Bioengineering Noninvasive Methods and Prosthetic Devices

New noninvasive methods must be developed for the assessment of cardiovascular function. A major problem is the detection of inapparent cardiovascular disease. Detection should be

possible on a population survey basis without the necessity of cardiac catheterization or other invasive maneuvers. Various methods using ultrasonic energy, radioisotopes, etc., should be developed to permit the early detection and quantification of abnormalities of coronary and cerebral blood flow and cardiac function. The development of these methods would facilitate community trials of preventive and therapeutic measures as well as community surveys for the detection of inapparent heart disease in adults and children.

There is a need to develop devices capable of fully substituting for the heart over long periods of time, as well as improved circulatory assist devices and artificial oxygenators for short-term support of the circulation.

New vascular prostheses, such as vessels and cardiac valves, which are particularly resistant to thrombosis, must be developed. Important bioengineering developments would include new devices for the detection of arrhythmias, improved pacemakers and defibrillators, and new approaches to intrauterine and neonatal surgery.

3.2.3 Behavioral Studies

Patient motivation and compliance appear to be major stumbling blocks in the prevention and treatment of diseases of the heart and blood vessels. Behavioral and motivational research is needed to discover the determinants of patient adherence and methods for insuring a higher degree of compliance to medication and other intervention efforts including cessation of smoking, diets, exercise, all of which have important bearing on successful patient management.



3.2.4 Animal Models

The development of relevant animal models for the study of cardiovascular diseases would support and assist studies of etiology and pathogenesis from the subcellular to the community group level. Animal models that simulate the human situation would be particularly helpful in testing preventive and therapeutic regimens and in determining complex interactions that occur in the whole organism in atherosclerosis, coronary heart disease, hypertension, stroke, and all other cardiovascular diseases under consideration. Animal models should be sought through exploration of new species, selective breeding, experimental manipulation, and surveys to discover naturally occurring animal disease models. Particular attention should be given to the development of nonhuman primate models because of their similarity to the cardiovascular system of man.

At present many forms of therapy have, on the basis of pilot studies, been shown to be of great potential usefulness. It is not possible to recommend widespread and general use until careful, controlled evaluation has been conducted. This approach is essential in order that the most appropriate methods of delivery be identified and that the true cost effectiveness of therapeutic programs be known. The human resources required include not only epidemiologists, biostatisticians and skilled clinical investigators, but also physicians, assistants, and community health aides in order to carry out large-scale trials.

3.3.1 Controlled Clinical Trials

Controlled clinical trials are needed to determine the effectiveness of modifying diet in retarding the progression of atherosclerosis or preventing atherosclerotic disease. Current evidence implicates diet as the most important environmental agent, but because of the drastic economic and industrial implications of changing the U.S. diet, recommendations for massive dietary changes await the conclusive evidence that controlled trials would provide.

Separate clinical trials should be designed to test the lipid hypothesis by observing the effect on the atherosclerotic process of lowering serum lipids by all available means (diet, drugs, surgery, etc.).

A separate clinical trial should evaluate the effect of modification of specific risk factors other than hyperlipidemia, such as elevated blood pressure and physical activity, on atherosclerosis.

3.3.2 Antihypertensive Therapy

Therapy of modest to severe hypertension has been demonstrated to be effective in reducing the incidence of stroke. It is now necessary to evaluate systems to detect hypertension and to deliver appropriate care over prolonged periods in large populations of patients. Demonstration programs must be established whereby the optimum role of nurses and other health care personnel can be defined. The effectiveness of treatment of patients with borderline hypertension must be determined before widespread application of therapy is recommended for the populations of patients with mild hypertension. An efficient system is needed for mass screening of early asymptomatic hypertension and for prehypertension in teenagers.

3.3.3 Antiarrhythmic Therapy Following Myocardial Infarction

Evidence from a number of centers throughout the world suggests that the mortality of patients who have recovered from an acute myocardial infarction might be reduced by chronic administration of antiarrhythmic therapy. It is not prudent to launch widespread community-based treatment programs until specific populations of patients most likely to be benefited are identified and the cost effectiveness is determined. The incidence of sudden death following myocardial infarction is relatively low; hence, large numbers of

patients would have to be treated to demonstrate effectiveness. It should, however, be possible to identify a small high-risk group of individuals for careful studies including long-term monitoring for the incidence of premature contractions and periodic provocative tests. The demonstration of a reduction in death rate in a particular subset of patients following myocardial infarction could have widespread implications.

3.3.4 Evaluation of the Effectiveness of Therapy Designed to Minimize the Extent of Myocardial Infarction

In the experimental animal, a number of pharmacologic, hemodynamic, and other procedures appear to reduce the magnitude of myocardial infarction which follows coronary occlusion. These procedures all depend upon a complicated interrelationship between coronary blood flow, myocardial oxygen consumption and other factors. There is, as yet, no experimental animal preparation for the study of myocardial infarction which will yield results clearly translatable to man. Therefore, these techniques must be subjected to careful evaluation under controlled circumstances in man. This type of evaluation would require development of better techniques for quantification of infarct size so that the effects of intervention can be clearly demonstrated.

3.3.5 The Surgical Therapy for Ischemic Heart Disease

Vein bypass graft surgery for coronary artery disease is effective in relieving the symptoms of angina pectoris in

85 percent to 90 percent of patients. The widespread application of this procedure is, however, also partially dependent upon the hope that life expectancy of patients is also being increased. Prospective random trials are currently underway to evaluate vein bypass graft surgery with respect to the duration and quality of life in a number of subsets of patients with ischemic heart disease. These programs should be encouraged and broadened.

3.3.6 Evaluation of Exercise Programs

Individuals with habitual high levels of physical activity appear to have a decreased incidence of and mortality from myocardial infarction. The enhancement of cardiovascular performance by exercise training has been demonstrated both in normal subjects and in patients with coronary artery disease. There is need for careful systematic evaluation of the physiologic, psychologic, sociologic and vocational effects of exercise on the prevention of coronary heart disease. The effect of exercise programs on, and the role of exercise in treatment and rehabilitation of, cardiac patients should also be evaluated.

3.3.7 Evaluation of Devices and Materials

There is need for continued study of devices designed to assist the failing circulation in shock and circulatory failure. The lack of a satisfactory animal model for these conditions makes it necessary to conduct the studies in man and the emergency nature of the situation renders clinical

investigation difficult. It is, however, essential that these devices be subjected to critical evaluation before they are released for use at the community hospital level.

3.3.8 Evaluation of Stroke Programs

Despite the widespread development of sophisticated facilities for the care of patients with acute strokes, this system of treatment has not been subjected to critical evaluation. There is need for scientific objective evaluation of the various therapeutic measures available. The role of hospitalization, outpatient care, and care in specialized facilities must be determined.

3.3.9 Evaluation of Therapy for Peripheral Vascular Disease

The medical and surgical therapy of peripheral vascular disease should be subjected to critical evaluation. Essential to such an evaluation would be the development of a standard system for characterizing the extent and severity of the disease. Newer methods employing ultrasonics and radioisotopes should be used to supplement clinical assessment.

3.3.10 Evaluation of Therapy for Cardiac Failure

The value of pharmacologic and mechanical methods that lower the impedance to left ventricular ejection in the treatment of cardiac failure requires careful evaluation.



3.11 Outpatient Diagnosis and Follow-up

Specialized centers should be developed so that high-risk individuals (especially patients with preexisting clinical coronary disease) can be carefully evaluated. These centers would provide for evaluation of long-term prognosis and also serve as emergency diagnostic facilities for patients with chest pain or other cardiovascular symptoms. The widespread application of this approach should be preceded by a careful evaluation of the effectiveness of these centers in reducing the incidence of sudden deaths, 60 percent to 75 percent of which occur outside hospitals. The need for the evaluation of such outpatient centers is based on studies showing that many victims of sudden death have been symptomatic prior to their death.

3.4 IMMEDIATE APPLICATION OF CURRENTLY AVAILABLE
KNOWLEDGE FOR THE PREVENTION, DIAGNOSIS,
TREATMENT AND REHABILITATION OF PATIENTS

The list of cardiovascular diseases for which proven effective therapy is available is relatively short, but the impact of these therapies would be great and relatively immediate. Therefore, implementation of these programs should receive high priority.

3.4.1 Prevention of Atherosclerosis in High-Risk
Subjects

Evidence relating coronary risk factors to the progression of atherosclerosis supports the development of an aggressive program of prevention and control in high-risk individuals, that is, persons who have hyperlipidemia and/or hypertension and who smoke. A "multifactorial intervention" program, designed to eliminate or reduce risk factors, in these high-risk patients in an effort to prevent premature atherosclerosis should be implemented through (1) public and professional education, (2) screening for high-risk individuals, (3) referral of high-risk individuals for consultation and treatment, and (4) follow-up of high-risk individuals to evaluate the effect of treatment. Special attention in this program should be given to the adolescent and young adult.

3.4.2 Treatment of Hypertension

The treatment of modest to severe hypertension will reduce the incidence of heart failure and stroke. This clearly indicates that vigorous therapy should be pursued in a large number of hypertensive patients who are not currently



receiving treatment. Screening programs should be developed for the detection of hypertension. Physicians should be made aware of the importance of therapy for patients with hypertension and be prepared to institute optimal care. Detection will not be effective unless followed up with treatment; therefore, centers must be developed to provide a long-term consistent program of therapy for the patient with hypertension. Therapy should be directed by experts who are aware of the available drugs and side effects and are prepared to change therapy to obtain the most effective results with the least side effects.

1.4.3 The Prevention of Rheumatic Fever

Rheumatic fever is unique among the major causes of cardiovascular disease in that it is almost completely preventable. It is possible to treat streptococcal infections and reduce the incidence of rheumatic fever and hence rheumatic heart disease. To effectively control rheumatic fever, it is necessary to conduct a widespread program of public and professional education. The physicians and the public must be aware of the dangers of undiagnosed and untreated streptococcal infection, and effective, inexpensive, accurate diagnosis, prophylaxes and treatment must be available. Of equal importance in the approach to the problem of rheumatic fever and rheumatic heart disease is environmental alterations to eliminate or reduce overcrowding, poor hygiene, malnutrition, etc., which appear to be associated with a high incidence of streptococcal infection and hence rheumatic fever.

3.4.4 To Decrease Morbidity of Congenital Heart Disease by Providing Early and Prompt Treatment in the Neonatal Period

This could best be accomplished by: widespread training of personnel in newborn nurseries to detect the child with congenital heart disease early in life, development of noninvasive diagnostic procedures to confirm the diagnosis; and development of facilities and a regional network whereby the infant can be transferred to a cardiac diagnostic and surgical facility for prompt correction. Surgical therapy is available for most forms of congenital heart disease if the patient can be brought into contact with the appropriate facility.

3.4.5 Improve System of Emergency Care with Widespread Application of Cardiac Resuscitation Outside the Hospital

The ultimate objective of this program is dissemination of information about the need for and the technique of administering cardiac resuscitation so that citizens would be able to provide resuscitation at any place and at any time. Special attention should be given to the training of the family of patients who have experienced a myocardial infarction or who are at high risk for another reason. Under ideal circumstances, patients would be given every chance of surviving acute arrhythmias or asystole. In addition to widespread training, this approach would require better methods of transportation, communication and ambulances equipped with telemetry, defibrillators and other necessary equipment.

PART IV

THE LEGISLATION AND THE PROPOSED PROGRAM



PART IV
THE LEGISLATION AND THE PROPOSED PROGRAM

Section 413 of the National Heart, Blood Vessel, Lung and Blood Act of 1972 delineates 10 specific program requirements. This section correlates the conclusions and recommendations of the Heart and Blood Vessel Diseases Panel and its Task Groups with the 10 legislative requirements.

Table 4-1 summarizes the response of all 91 recommendations (see Part V) to the legislation. There is great overlap among the recommendations prepared by different Task Groups and also among the 10 points of the legislation. Therefore, it would serve no purpose to attempt to document all the possible relationships between the legislative points and specific recommendations. For example, almost all recommendations apply to legislative points 7 and 8 which are concerned with training, as trained persons are required for the implementation of all parts of the program. Therefore, these sections are often blank in Table 4-1. This section is designed to give the reader a few examples of recommendations



Table 4-1
DISTRIBUTION OF TASK GROUP RECOMMENDATIONS
WITH RESPECT TO THE TEN LEGISLATIVE POINTS IN THE ACT

Legislative Point	Task Group										
	Athero- sclerosis	Coronary Heart Disease	Peripheral Vasc. Disease	Hyper- tension	Stroke	Congenital Heart Disease	Rheumatic Heart Disease	Cardio- myopathy	Arrhythmia	Cardiac Failure	Shock
1 Epidemiology, Etiology	5.1.1, 5.1.3 5.1.4, 5.1.8	5.2.1	5.3.1, 5.3.5	5.4.9, 5.4.10 5.4.11	5.5.1, 5.5.3 5.5.4, 5.5.5	5.6.2, 5.6.4	5.7.1, 5.7.2 5.7.5, 5.7.6 5.7.8, 5.7.9	5.8.1, 5.8.3 5.8.7	5.9.3	5.10.1, 5.10.3	
2. Biological Processes	5.1.1, 5.1.3	5.2.2, 5.2.3 5.2.4	5.3.2	5.4.5, 5.4.6 5.4.7, 5.4.8 5.4.12, 5.4.13	5.5.4, 5.5.5 5.5.7	5.6.2, 5.6.3 5.6.4	5.7.3, 5.7.9	5.8.2, 5.8.7	5.9.1, 5.9.2 5.9.5	5.10.1, 5.10.2 5.10.3, 5.10.7	5.11.1, 5.11.2 5.11.3, 5.11.5
3. Techniques, Drugs, Devices	5.1.9	5.2.7	5.3.4, 5.3.6 5.3.8	5.4.1, 5.4.2	5.5.2, 5.5.6	5.6.1, 5.6.4 5.6.5	5.7.1, 5.7.2 5.7.3, 5.7.7 5.8.7	5.8.3, 5.8.6 5.8.7	5.9.1	5.10.1, 5.10.4	5.11.3, 5.11.5 5.11.7, 5.11.8
4 Bioengineering	5.2.5	5.2.5, 5.2.6 5.2.8	5.3.2, 5.3.3 5.2.5		5.2.5	5.6.1	5.7.1, 5.7.2 5.7.4	5.8.4	5.9.6	5.10.1	5.11.5, 5.11.6 5.11.7
5. Field/Clinical Studies	5.1.2, 5.1.5 5.1.6, 5.1.7	5.2.8, 5.2.9	5.3.8	5.4.1, 5.4.10		5.6.4	5.7.7	5.8.4, 5.8.6	5.9.4, 5.9.5	5.10.5	5.11.10
6. Blood Resources		5.2.2			5.5.5						
7. Specialist Education			5.3.7	5.4.1						5.10.6	5.11.9
8 Public Education	5.1.10	5.2.8 5.2.9	5.3.9	5.4.1, 5.4.4		5.6.1	5.7.6	5.8.5	5.9.7	5.10.5	
9. Childhood Diseases	5.1.5			5.4.3		5.6.1	5.7.1, 5.7.2 5.7.6, 5.7.7				
10. Emergency Services		5.2.8				5.6.1			5.9.7	5.10.5	5.11.8

which are addressed specifically to a point in the legislation. Each of the 10 points is listed and discussed separately in the following subsections.

A complete listing of the requirements is found in Appendix B. Two sets of figures are also included in Appendix B. One of these sets depicts, on a Task Group basis, the percentage of project areas applicable to each of the 10 legislative planning requirements. The other set is similar but relates to the four objective categories. Included with both sets is a composite figure illustrating the distribution for all Task Groups.

A listing of problems, approaches and project areas is given in Appendix C.



"... investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases; ..."

The Panel report stresses the importance of understanding the etiology of atherosclerosis and hypertension as the key to the prevention of coronary disease, stroke and peripheral vascular disease. Prospective epidemiological studies are recommended to determine the importance of newly identified risk factors and genetic traits in the development of atherosclerosis.

Based on previous epidemiological and clinical studies, it is now possible to identify individuals at very high risk for a heart attack. The Atherosclerosis Task Group recommended that a major effort in multifactorial intervention in high-risk subjects should be conducted.

Other risk factors for atherosclerosis should be sought, especially psychosocial factors and behavior types. Further research was also suggested to determine the importance of various environmental factors such as carbon monoxide trace substances, and the composition of drinking water. The relationship between smoking and progression of the disease is well recognized but the mechanism whereby it exerts its effect requires elucidation. There is a need both for prospective studies to determine the importance of risk

factors and designed clinical trials for evaluating the effectiveness of modification on the frequency of disease.

The Atherosclerosis Task Group along with several others mentioned the importance of social and behavioral studies to the prevention of disease. Better and more effective methods need to be devised to modify smoking, diet, and to insure adherence to medication. Patient motivation to take the essential medication is required in the management of hypertension and rheumatic heart disease.

A universally acceptable system of classification of patients with coronary heart disease based on clinical and laboratory data is needed. Such a system would facilitate the conduct of epidemiological studies, prevention trials, and the evaluation of therapeutic measures such as the medical and surgical procedures designed to reduce the mass of ischemic myocardium.

The key role of precipitating factors in the etiology and pathogenesis of coronary artery disease, stroke, transient ischemic attacks, and peripheral vascular disease was noted. Atherosclerosis is the underlying disease process in all three conditions, but an additional factor or factors superimposed upon the vascular process produces the critical degree of narrowing which eventuates in ischemia and the permanent loss of tissue. Thrombosis and embolism are cited as precipitating factors, but there are probably many others which require investigation. The control of these precipitating factors would result in the prevention of many of the consequences of atherosclerosis. Epidemiological studies of sudden death are needed to identify groups of individuals



prone to ventricular fibrillation or asystole. Provocative tests may be needed in such a survey. This approach to the problem of sudden death begins with the identification of the population at risk. High-risk populations, so identified, could be used for the trial of preventive medication or devices. Studies of the epidemiology of coronary heart disease and sudden death are also essential to the design and organization of emergency services.

Epidemiological studies of the incidence and occurrence of hypertension in various population groups are cited as sources of useful information about the etiology of coronary artery disease and may provide clues to the basic mechanism of the disease. Investigation of the viral, genetic and teratogenic factors in the etiology of congenital heart disease are encouraged. Prospective epidemiological studies in high-risk populations should receive high priority. It is possible that investigation in this area might lead to the discovery of etiological agents which if eliminated would substantially reduce the incidence of congenital heart disease.

Great progress has been made in the prevention of rheumatic fever by the treatment of streptococcal infections. Further knowledge is needed about the biological properties of the streptococcus and the immunological response of the heart to the organism. This improved understanding of the etiological agent could be applied to yield more rapid, accurate, and inexpensive methods for the diagnosis of streptococcal infections. Additional benefits would be the development of more effective antistreptococcal antibiotics which could be used in the early treatment of the infection and hence prevent



rheumatic fever. An antistreptococcal vaccine could be the ultimate result of these basic studies, and could lead to the elimination of rheumatic fever.

Investigation into the etiology of nonrheumatic valvular disease is also indicated. Special attention should be given to the cardiovascular complications of drug abuse. The role of alcohol, nutritional and behavioral factors in the etiology of cardiomyopathy were identified as areas of importance. Animal models would be useful in these studies of the etiology of cardiomyopathy.



"... studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena; ..."

The prevention and/or treatment of diseases of the heart and blood vessels depend upon a full understanding of normal physiological and biochemical function. Only with extensive knowledge of the normal processes can functional abnormalities caused by disease be understood.

4.2.1 Function of Blood Vessels

Knowledge of the physiology and biochemistry of vascular smooth muscles and the role of humoral and neural mechanisms involved in the control of the arteries and arterioles is of utmost importance to the understanding of vascular disease, such as atherosclerosis, coronary artery disease, stroke, peripheral vascular disease, hypertension and shock. The process whereby the blood flow is regulated in different vascular beds such as heart, brain, kidney, intestine and skeletal muscle needs to be better understood. The interaction of circulating hormones with their receptors in blood vessels as well as control of blood vessels by the nervous system must be elucidated.

There are a number of vasoactive drugs currently in use whose mechanisms of action remain unknown, e.g., the means whereby nitroglycerin relieves angina pectoris is still under investigation.

4.2.2 Collateral Vessels

The development of collateral blood vessels is another important area for research, particularly in the heart, brain and peripheral tissues. Knowledge of the mechanisms involved in the growth of collateral vessels could lead to ways of increasing blood flow to ischemic or potentially ischemic tissues.

4.2.3 Metabolism

New knowledge about the metabolism of tissues, such as brain and heart, is needed to understand the changes that take place with ischemia. For example, the brain does not show enhanced de novo synthesis of ATP during periods of ischemia (in contrast to heart and kidney) and possibly this may be in part responsible for the low tolerance of the brain to ischemia. The importance of cell swelling in bringing about irreversible changes following ischemia needs to be documented, especially with respect to the role played by impaired cellular ion transport. One of the principal risk factors in the genesis of atherosclerosis is hyperlipidemia. A better understanding of lipid metabolism in the vessel wall and the responses of the vessel wall to stress and high lipid concentration will yield insight into the genesis of atherosclerotic lesions.

4.2.4 Growth and Hypertrophy of the Heart

New knowledge is needed concerning protein synthesis and its control in the heart under conditions of normal growth and

how these are altered by such conditions as hypertension and heart failure in the production of cardiac hypertrophy.

4.2.5 Membrane Function in the Cardiac Wall

Rational treatment and prevention of cardiac arrhythmia requires intimate knowledge of processes such as excitation, conduction, ion movements and their relationship to resting and action potential, as well as the mechanisms of action of certain drugs in modifying these processes.

4.2.6 Fluid Balance and Microcirculation

The factors responsible for fluid exchange and how these are altered by changes in blood pressure, venous pressure, osmotic pressure, renal function, and circulating toxic factors must be studied in heart failure and shock, where tissue hypoperfusion and abnormalities of fluid distribution occur. Toxic factors which may be important in shock should be identified and their action investigated.

4.2.7 Control of Cardiac Contraction

In order to understand heart failure, it is necessary to elucidate the complex cardiac cellular metabolism, energy sources, the function of the contractile elements, cellular ion transport, excitation-contraction coupling and the regulation of contractile protein interaction involved in the normal contractile process. The important regulatory role played by catecholamines and other hormones and the interaction of these hormones with their receptors must be understood. Studies of the neural control of cardiac function are also of great importance in providing a basis



for better understanding of the way in which stress and other environmental factors exert their influence. This information is also essential for a better understanding of the action of therapeutic drugs, such as digitalis, on myocardial contractility.

4.2.8 Rheumatic Fever and the Immune Response

The complete conquest of rheumatic fever will require additional knowledge of the immunologic processes responsible for the development of the disease. Such studies may lead to the development of a useful vaccine.

4.2.9 Cardiac Function of the Infant and Fetus

In order to deal effectively with congenital heart disease, we must understand how the fetal circulation changes to the adult form. The development of the cardiovascular system in utero must be understood so that the adverse effects of certain drugs and viruses may be prevented.

4.2.10 Animal Models

In investigation of normal and abnormal cardiovascular function, it is essential to have suitable animal models. Efforts should be expended in developing such new models and also exploiting existing animal models produced by nature.

"... research into the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases..."

Research into the development of drugs, techniques and devices for the prevention, diagnosis, treatment and rehabilitation of patients suffering from heart and blood vessel diseases represents a major portion of virtually all of the recommendations of the individual task groups. In many cases these would follow directly from studies of prevention, epidemiology and etiology, and from research into the basic biological mechanisms of these diseases (Legislative Requirements 1 and 2). In addition to the many biomedical science approaches to these objectives, the social science approach to compliance with good health measures and optimal living conditions in the prevention and treatment of hypertension, streptococcal infections and rheumatic fever and the rehabilitation of such patients is an important area for research. The effect of commonly used drugs and alcohol consumption on cardiomyopathy and in its relationship with nutrition deserves further investigation. A fundamental epidemiological question in the field of arrhythmias is whether the arrhythmias are independent risk factors or just a measure of the severity of the underlying atherosclerosis. If the former is the case, well organized drug trials would appear to be in order.



Hypertension is the cardinal risk factor for stroke and also a major determinant of coronary heart disease. Many strokes could probably be prevented by a more vigorous preventive program for the identification and treatment of hypertension. The specific etiology of hypertension should be sought. The possible genetic and environmental factors that determine the higher prevalence of high blood pressure among blacks should be studied. Consideration must also be given to the further identification of the importance of multilevel factors, especially salt and obesity, and psychosocial variables as determinants of elevated blood pressure especially in relation to specific genetic factors.

The need for a better mechanism whereby new forms of diagnosis, therapy, prevention, and rehabilitation can be subjected to critical evaluation before they are introduced into widespread use was highlighted by several Task Groups. This is especially true of those diseases related to atherosclerosis: coronary heart disease, peripheral vascular disease, and stroke in which clinical trials must be conducted in man. Problems in conducting clinical trials are often related to the premature acceptance of the preventive, diagnostic or therapeutic modalities so that the timing of clinical trials is critical. The trials must be conducted before the intervention has received widespread acceptance, yet delayed to a point sufficiently far along in its development that the need for a costly evaluation is clear once the safety of the technique, drug or device is established. Although costly to conduct, such trials would save large sums of money if, indeed, the intervention turned out to be of little practical value.



The need for a new strategy with regard to evaluation of therapy is apparent from a critical look at recent developments. Many drugs are now being employed on a long-term basis to reduce the probability of subsequent morbidity and mortality; for example, to reduce serum lipids in patients with certain hyperlipidemias and blood sugar in patients with diabetes, even though proof is lacking that correcting these aberrations of blood chemistry lessens the probability of death and disability. Similarly, surgical therapy of coronary artery disease, which unquestionably relieves angina pectoris, must be examined to determine whether life is being prolonged. Many of the Task Groups recommended the implementation of programs for the improved delivery of cardiovascular health care, as for example in the case of hypertension. Such new modes of health care delivery require the same critical controlled evaluation as do specific drugs and surgical approaches.

A continuing panel within the National Heart and Lung Institute is needed to formulate and implement the strategy for the evaluation of therapy. This panel should operate in close cooperation with the Food and Drug Administration (FDA), and should include NHLI staff, members from the Office of Scientific Evaluation of the Bureau of Drugs of the FDA, scientists with experience in trial design, biostatisticians, clinical pharmacologists, and experts in the appropriate disease areas and therapeutic modalities. Effective levels of support should be provided to the Cardiovascular Division of the Bureau of Drugs of the FDA so that the development, testing and evaluation of new and promising drugs will be encouraged and expedited. The resources and staff of the FDA should be maintained at a high level so that close and



continuing relationships with scientists, physicians, and related agencies will be fostered. There is also need in the National Heart and Lung Institute for a panel or group responsible for clinical trials and the organization of coordinated data collection centers.

An appropriate mechanism should be created within the NHLI for the support of programs concerned with the development of therapeutic devices. All too often such programs are not considered suitable for research support and are still not far enough along to be attractive to industry. This intermediate stage in development should be supported to fill the gap between the completion of basic research and the production of a device by industry. Industry should be encouraged to develop new drugs and devices by facilitating review and approval mechanisms.

Many of the planned epidemiological studies will depend upon the development of improved techniques of measurement of etiological factors such as diet, behavior, and physical exercise. Better methods of measurement of specific pathological processes such as the localization and type of vessel stenosis and the quantification of myocardial ischemia are needed. A standardized system for the classification of patients with coronary artery and cerebral vascular disease is required for the conduct of collaborative studies. This system should include the potential for computer storage of clinical information for retrieval and machine processing.



"... establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases; ..."

Computer facilities, perhaps centralized on a regional or national basis, are needed with respect to the study and analysis of large population groups. This is particularly relevant to the problem of atherosclerosis with respect to the contribution of lipid levels, geographical location, physical environment, cigarette smoking, physical exertion, dietary constituents, and other factors. Reduction of a mass of data is necessary to identify the nature of significant contributory factors and in the study of predisposing factors or efficacy of treatment in coronary artery disease, peripheral vascular disease, stroke, hypertension, rheumatic heart disease, arrhythmias, and shock. The development of instruments and central laboratory facilities would be used in the rapid screening of blood lipid parameters, in the diagnosis of streptococcal infections, in the identification of viruses, and in the determination of the plasma concentrations of cardioactive drugs.

A major bioengineering effort is needed in the development of noninvasive methods for studying the state of blood vessels in the body, such as the peripheral limbs, the brain, and the heart, as well as noninvasive methods for assessing accurately structure and function of the heart. The development of a



system whereby the vascular tree could be mapped by non-invasive means would represent a major advance. If potentially occlusive lesions in the cerebral and coronary circulations could be identified simply and without hazard there would be a great acceleration in the rate of progress toward treatment of coronary heart disease and stroke. If lesions could be detected before they produce symptoms, interventions could be evaluated at an early stage in the disease. The effect of dietary and drug regimens on regression of early atherosclerotic lesions could be studied. The role of surgical procedures to bypass the obstruction could also be assessed more readily.

Improved portable devices for the detection and recording of arrhythmias in ambulatory patients as well as the electrical correction of arrhythmias are recommended. Methods for specifically assessing blood flow to various organs, particularly the lungs and viscera, are needed. Automated devices for continuously monitoring coagulation parameters would be most desirable.

Considerable further research is needed in the development of mechanical devices for augmentation of the function of the failing heart as well as devices which may totally replace it. The development of better methods for intravascular manipulation and possibly surgery would be of value in the treatment of occlusive disease of the heart and the central nervous system.

The in utero diagnosis of congenital heart disease will require better, more automated methods for examining amniotic fluid and better noninvasive techniques for



assessing the physiologic function of the fetus. Improvement in the design of prosthetic valves, particularly with respect to their surfaces, is emphasized. Better methods are required for the in vivo localization of thrombi as well as in vitro tests of clotting parameters as previously indicated. Implanted pacemakers require improvement with respect to size, reliability, automatic application, and miniaturization as well as the development of more long-lived practical power supplies.



"... establishment of programs for the conduct of direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases; ..."

Many of the Task Groups have recommended that field studies should be planned.

These studies include:

- Longitudinal approaches to determine the relationships between risk factors and disease, for example, environmental or behavioral variables related to the development of coronary artery disease.
- Programs to deliver an effective therapeutic modality to the community by identifying and treating high-risk individuals including (a) treatment of hypertension and (b) prevention of rheumatic fever by identifying and treating streptococcal infections.
- Improvement of care during an acute disease episode such as the evaluation of the best approaches for the care of patients with stroke or the emergency care of acute myocardial infarction and potential sudden death.
- Clinical trials to determine the effectiveness of modification of variables or processes on the incidence and natural history of disease including (a) the effects of dietary modifications on the incidence of chronic cardiovascular disease, (b) the effectiveness of treatment of mild hypertension and (c) the value of coronary artery bypass surgery.

The conduct of these field studies will require a substantial increase in personnel, especially in epidemiology, biometry,



clinical pharmacology, behavioral sciences, clinical medicine and surgery. Centers with the requisite expertise for organizing these studies are badly needed. Additionally, a much more favorable climate for clinical trials and field studies should be developed through better education of physicians and the public about the value of these studies and the necessity of clinical testing in man prior to widespread application.

Many Task Groups also recommended special attention to rehabilitation. Rehabilitation is defined as the sum total of efforts required to return a patient toward normal living. It is a relatively new concept in the area of cardiovascular disease. Rehabilitation efforts are directly dependent upon the prior success in returning patients with many types of cardiovascular illness toward adequate functional levels. It is only for this reason that rehabilitation deserves specific delineation, because, in practice, rehabilitation is inseparable from the concepts and the programming of comprehensive management and treatment of patients with cardiovascular disease. The emphasis of rehabilitation is on assessment of function. For all forms of cardiac disease, physicians and health care personnel must be taught the systematic medical evaluation of functional impairment (to be distinguished from disability, which is a legal determination). Rehabilitation concerns the level of function which must be correlated with recommendations for career choice and for the level of physical activity at work. Rehabilitation must take account of the indication for both medical and surgical intervention and possibly the prognostic elements; it also emphasizes the enhancement of physical function by medical and surgical therapy and by training; the enhancement of educational and vocational function by appropriate



training; and the enhancement of psychologic function involving mechanisms by which the patient is able to cope with illness and impairment.

Furthermore, rehabilitation interests are not strictly vocational. Rehabilitation for many patients with cardiovascular disease, particularly older patients not in the work force, involves the ability to live independently.

For all rehabilitative efforts, industry is an ideal site for:

- Screening procedures
- Public education
- Intervention via industrial medicine programs
- Function evaluation regarding hiring or rehiring of cardiac patients--with attention to suitable job placement.

"... studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products; ..."

The close relationship between atherosclerosis and thrombosis was emphasized by many Task Groups. The interface between the vessel wall and the flowing blood was considered to be a primary target area for collaborative research. Thrombosis and embolism when superimposed on atherosclerosis are responsible for heart attack, stroke, and peripheral vascular disease. If it were not for thrombosis, atherosclerosis would have less impact on life expectancy. The importance of this area is reflected in the fact that a specific panel was established to consider Blood Diseases.



4.7 LEGISLATIVE REQUIREMENT NO. 7

"... the education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases; ..."

The large increase in effort in the conquest of cardiovascular diseases as envisioned in the National Heart, Blood Vessel, Lung, and Blood Act of 1972 cannot be implemented without the availability of adequate trained manpower. Education and training, along with basic research, are fundamental to long-range progress. Facilities and equipment are meaningless unless utilized effectively by motivated, dedicated and highly trained personnel. Discoveries which will result in breakthrough in the problems of atherosclerosis and hypertension, similar to that which has eliminated poliomyelitis, are made by trained scientists. New therapeutic procedures and devices can only be tested and evaluated by clinical investigators skilled in the application of scientific discipline to the assessment of results in patients. Lastly, implementation of the plan and the delivery of the final product to the community requires physicians, nurses and other allied health professionals.

Training, like the acquisition of new knowledge through research, represents an investment in the future which cannot be ignored. The long-term needs for personnel at all levels must be determined and training programs matched to this need. Training is a slow, long-term process. Conversion of a medical school graduate into a trained cardiovascular clinical investigator requires at least five years of



specialized study beyond medical school; therefore, advanced planning is essential. The training process is long. It is also necessarily inefficient because identifying with certainty those individuals who have research potential is impossible at the inception of the training program. Imaginative, talented individuals are rare and can only be recognized by observing their performance under the influence of a favorable environment.

A wide variety of highly trained persons will be required for the implementation of these new programs. Scientists must be trained in order to carry out the research recommended by this report. A pool of trained scientists with competence to approach the wide variety of problems relevant to cardiovascular diseases is not presently available. Epidemiologists, clinical investigators, peripheral vascular clinical specialists, experts at designing and running clinical therapeutic trials, pharmacologists, pathologists, physiologists, biochemists, and electrical engineers are all needed.

Individuals must be attracted to the area of cardiovascular research both at a graduate level and at a postgraduate level by the continuation and expansion of the NHLI support of training programs for investigators. Clinical training in certain areas where specific shortage exists as, for example, in peripheral vascular disease, must be continued. The stable support of established young scientists and teachers must also be provided. In addition to scientists, the implementation of the treatment and demonstration programs envisioned requires the use of substantial numbers of allied health professionals. For example, programs for the detection and treatment of hypertension in the community can only



be executed with a large number of allied health professionals. The problem of community information and motivation also requires health volunteers who will provide a network to deliver the health message to the people.

The stable support of senior medical scholars is also essential to the training effort. These persons provide the continuity in research, teaching and training which will continue to be required for the direction of large-scale programs. There is a particular need for stable support of senior scholars concerned with all aspects of disease prevention, an area all too often emphasized less than treatment in our medical schools.

Continuing education at all levels must not be ignored. As new information becomes available, it must be delivered to the practicing physicians and allied health professionals. An effective process of information-renewal and updating is required. The training process never ceases; therefore continuing education must be built into any delivery system.



"... public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources; ..."

There is a great need for enhanced public and professional education in order to deliver health care successfully now and in the future. Professional education of physicians relates first to the primary care physician and second to the specialist. The generalist must be given an enhanced awareness of the many concrete advances which he can now apply to the effective prevention of disease in areas such as control of hyperlipidemia, treatment of hypertension, the recognition and treatment of congenital heart disease, and the recognition and prevention of rheumatic fever, to cite a few examples. It should be noted, as indicated previously in this report, that although rheumatic fever is largely preventable through the treatment of streptococcal infections with penicillin, there has been only a 30 percent decrease since 1930 and only one in five hypertensive individuals is presently under adequate therapy.

Specialists in cardiovascular diseases are needed with continually upgraded education and experience in highly sophisticated and evolving areas of knowledge. They have a key role in advanced diagnostic techniques and surgical treatment and in the complex medical therapy of some disorders. They also serve a role in clinical investigation.

The level of awareness and effectiveness of training of paramedical personnel will often determine the success of



evaluative or preventive programs. Such individuals are valuable in the detection of congenital heart disease, the control of hypertension, the implementation of field trials to prevent atherosclerosis, and in implementing cardiopulmonary resuscitation programs.

Public education is needed in all areas of cardiovascular disease. Coronary artery disease requires particular emphasis since death from arrhythmic complications can often be prevented by the prompt application of sophisticated treatment methods. The patient must be taught to seek these methods at the earliest onset of symptoms. Public education must be extended in this area to police forces, fire departments, and hospital staffs. Another kind of problem in public education relates to chronic diseases, such as hypertension, which are asymptomatic, yet which carry a considerable risk of disability and death. Public education must be directed at encouraging individuals to enter screening and treatment programs, if necessary, with respect to such chronic illnesses.

Health education of the public is itself an area in need of research and evaluation. It is by no means clear that we know the best educational methods that will enable a patient or the public to make decisions knowledgeably and effectively about his cardiovascular health. Without such knowledge, therapy and prevention will inevitably fall short of their potential benefits.



"... establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases; ..."

Prevention of Congenital Heart Disease is a goal which can be attained by pursuing the clues provided by known causes of the disease such as viral and teratogenic agents as well as genetic factors. Development of vaccines, antiviral chemotherapy and avoidance of teratogenic drugs will aid in the elimination of the disease. Early recognition of the disease in infants and rapid transfer of the sick babies for diagnosis and presently available treatment would result in the saving of thousands of lives. The understanding of the basic mechanisms of normal and abnormal function of the developing cardiovascular system would significantly improve diagnosis and treatment. Further improvement of standard diagnosis and surgical therapy and application to the problem of the neonate and fetus in utero will result in further reduction of mortality. The rehabilitation of the patient after surgery and the habilitation of the child with mild disease is essential to ensure a useful and productive life.

Initial and recurrent episodes of Rheumatic Fever can be prevented by implementing currently available methods to diagnose, prevent and treat streptococcal infection. However, more rapid, accurate and inexpensive methods are needed to diagnose streptococcal infection. The disease could be prevented by the development of an effective antistreptococcal vaccine. Risk factors need to be identified for the

development and recurrence of rheumatic fever. The behavioral and motivational factors in patient compliance with recommended medical care need further evaluation.

Persons who are at high risk to develop Atherosclerosis need to be identified early in life since the potential for prevention is greatest in the young. An intensive study is needed to evaluate risk factors in children. Greater efforts are needed to reduce cigarette smoking by the young and to prevent the acquisition of the habit.

The prevalence of Hypertension in children and adolescents needs to be determined and the blood pressure characteristics of the young must be defined precisely. It is important to know whether the course of essential hypertension can be altered if treatment is begun early in life.

It is important to recognize that diseases which affect infants and children and their responses to these diseases are significantly different from that of the adult. Therefore, the universal application of diagnostic techniques and therapeutic interventions to all age groups is not feasible. Instrumentation needs to be developed for specific use in children for evaluation of cardiac function and for arrhythmia and blood pressure monitoring. Devices are also needed for permanent pacemaking and short- and long-term circulatory assistance. The difference of the response of the young to newly developed drugs needs continuing emphasis.

"... establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessional in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services."

A cardiac emergency care system should be part of a general emergency care system, organized in accordance with the geographic and population structure of the region. It should involve an integration of all health facilities in that region, and include hospital emergency rooms and special stations in areas of high population density, such as sports arenas and industrial plants. All of these facilities should be linked one with another and with the mobile vehicle's communication system. The vehicle selected must be suitable to the region; in certain areas helicopters may prove to be the most efficient mode of transport. The communication system must be capable of transmitting electrocardiographic information to central stations where it can be interpreted and advice given to the personnel in the vehicle. There is need for more inexpensive, durable, and compact emergency equipment to include defibrillators, monitoring devices, and communication systems.

Not every hospital in a given region should be equipped with mechanical assist devices for the treatment of shock and myocardial infarctions, but these devices should be available in certain facilities appropriately distributed in the region. The same might be said for the specialized facilities for the care of infants with congenital heart disease. Therefore, the emergency transportation system must be organized so that patients with certain problems can be taken to the appropriate specialized facility.

The satisfactory function of any emergency system depends upon public education. The citizens must know of the existence of the emergency systems, how to call it, when to call it, and what to do until the emergency team arrives. Firemen, ambulance attendants, physical education instructors, first aid personnel in factories and persons completing first aid courses, should become adept at cardiopulmonary resuscitation. Special instruction should also be made available to the families and associates of patients known to be at high risk, for example, patients who have had one myocardial infarction. If this program of instruction for selected individuals is successful it might be broadened to include the general public. This certainly would decrease the possibility of a person dropping dead in the presence of another individual who did not know how to take appropriate action.

Caution is in order concerning the widespread application of systems which are as yet unproven. An effort should be made to develop demonstration units in which systems can be tested before they are recommended for widespread use.



PART V

INDIVIDUAL TASK GROUP RECOMMENDATIONS





PART V
INDIVIDUAL TASK GROUP RECOMMENDATIONS

This section collates the primary program recommendations made by the 11 Task Groups of the Heart and Blood Vessel Diseases Panel. The Task Groups and the number of recommendations of each are listed below:

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Coronary Heart Disease	-	9
Peripheral Vascular Disease	-	9
Hypertension	-	13
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Rheumatic and Other Valvular Heart Diseases	-	9
Cardiomyopathy	-	7
Arrhythmia	-	7
Cardiac Failure	-	7
Shock	-	10



1. Define more completely the pathogenesis of atherosclerosis in terms of cellular biology, the chemistry of macromolecules, interactions of the arterial wall and elements of the circulating blood, the role of the hemostatic mechanism, and conditions that influence progression and regression of lesions.
2. Conduct controlled clinical trials to determine the effectiveness of specific risk factor reduction and environmental modification in retarding the progression of atherosclerosis and preventing clinical atherosclerotic disease. These specific trials should include the following:
 - Diet modification in closed and free-living populations
 - Serum lipid reduction by whatever methods are available--diet, drugs, surgery, or other methods that may be devised--to test the "lipid hypothesis"
 - Other specific risk factor modification, particularly hypertension.
3. Determine the mechanisms of biochemical, genetic and behavioral control of blood lipids. Present research results are approaching the explanation of how lipoproteins are secreted into and removed from the plasma. There are many promising new fields of investigation including that of the role of behavioral factors in controlling blood lipids. Knowledge obtained through such research can lead to specific, rational methods for controlling hyperlipidemia.
4. Identify missing risk factors and etiologic agents. New prospective and experimental studies are needed to test specific hypotheses regarding yet unproven risk factors such as derangements of the hemostatic mechanism and behavioral traits. Genetic analyses should aid in identifying new risk factors and specific biochemical markers should be sought. Intensive study of risk factors in children is needed to identify persons at high risk as early in life as possible.

5. Identify individuals at high risk (hyperlipidemia, hypertension, smoking), and, through professional and public education, screening, referral, and follow-up, attempt to prevent atherosclerotic disease by "multifactor intervention." Give special attention to the adolescent, since the potential for prevention is greatest in the young.
6. Devise effective behavioral intervention methods to modify smoking, diet, adherence to medication, and other behavioral patterns identified as affecting risk of atherosclerosis.
7. Develop better hypolipidemic regimens such as drugs, foods, altered habits, surgical procedures, or other means of intervention that will lower serum lipids. Knowledge of the biochemical control of serum lipids and lipoproteins will contribute to such development. Foods low in cholesterol and saturated fat should be made available for high-risk persons and for clinical trials.
8. Intensify efforts to reduce cigarette smoking and particularly to prevent acquisition of the habit by the young.



1. Conduct studies concerned with the prevention of coronary atherosclerosis and hypertension. (See 5.1 and 5.4)
2. Study the mechanism of action of factors which precipitate myocardial ischemia, acute myocardial infarction, and sudden death to include studies of the interface between the blood and blood vessel wall, studies of collateral circulation development, the regulation of blood flow and drug action on the interaction between the vessel wall and the flowing blood.
3. Study the metabolic, mechanical and electrophysiological properties of the ischemic myocardium with special attention to the pathogenesis of arrhythmias and the protection of the ischemic myocardium.
4. Develop an animal model for myocardial infarction, sudden death and arrhythmia due to coronary arterial disease to expedite and accelerate progress with regard to the development and testing of preventive and therapeutic agents, devices and surgical procedures.
5. Develop simple, safe, rapid, noninvasive methods for the detection and quantification of coronary atherosclerosis.
6. Develop techniques for the quantification of myocardial ischemia which could be used in trials of medical and surgical therapy.
7. Evaluate currently available methods of therapy, for example antiarrhythmic prophylaxis, drug therapy for angina pectoris and myocardial infarction, and surgical therapy for angina pectoris.
8. Improve methods of providing emergency medical services including public education concerning the early warning symptoms of ischemic heart disease and widespread training in basic resuscitation procedures. Patients known to be at high risk, and their families, should be given specific instruction concerning the avoidance of the delay between the onset of premonitory symptoms

and the seeking of medical aid. A coordinated community emergency service should include a transportation and communication system and associated life support stations.

9. Improve the rehabilitation of cardiac patients which depends upon the education of physicians, industry, insurance companies, compensation boards, and the general public. These groups must learn that most patients with coronary heart disease can return to work and that cardiac function can be determined by objective tests and utilized in making work recommendations.



1. Determine how to prevent the development of atherosclerosis of peripheral vessels (5.1).
2. Develop noninvasive techniques for the localization of atherosclerotic lesions, quantification of their severity and the measurement of blood flow.
3. Develop improved prosthetic or biological vascular substitutes.
4. Determine the mechanisms which control the development of collateral circulation. Study the factors which regulate vascular smooth muscle. Determine the sites of action of vasoactive drugs.
5. Determine the mechanism by which diabetes, smoking, and hypertension promote the atherosclerotic process in peripheral vessels.
6. Standardize nomenclature and treatment programs by characterizing the extent, location, and type of disease with respect to therapy. Cooperative trials would be facilitated by this standardization.
7. Develop trained specialists (such as clinicians, allied health professionals, and basic investigators) in peripheral vascular disease to work as teams in medical centers and thus improve education and delivery of care.
8. Establish definite criteria for rehabilitation and job retraining for those afflicted with peripheral vascular disease. Identify occupational factors that might be important in retarding progression of peripheral vascular disease: environmental temperature, position of motion requirements of a particular job, etc. Early detection of peripheral vascular disease and patient education regarding disease management are the main rehabilitation components.
9. Begin national efforts through public education regarding both the early signs of peripheral vascular disease and relevant risk factors.



1. Educate physicians, special nurses, health care personnel and the general public in the great value of thorough, persistent, and skillful treatment of hypertension. Then develop optimal methods for bringing large numbers of hypertensive patients under adequate, continuous, long-term treatment.
2. Develop and facilitate the release of better drugs to combat hypertension and provide assistance as needed, to the Food and Drug Administration to attain this goal.
3. Determine an efficient system of mass screening for early asymptomatic hypertension and for "prehypertension" in teenagers. Therapeutic trials with regard to treatment of borderline hypertension are also needed. The effect on strokes, coronary heart disease, and sudden death should be particularly noted.
4. Train physicians, special nurses, and scientists to accomplish the research and treatment objectives of the hypertension problems.
5. Study the kidney as a regulator of arterial pressure, including the role of the renin-angiotensin-aldosterone system, and how it meshes with the central and autonomic nervous system in the total regulation of blood pressure and cardiac output. The effect of decreased renal mass on arterial pressure is another question to be answered.
6. Study intrarenal pressures, flows, and the distribution of pressures and flows that constitute signals for regulation of the secretion of various renal hormones--both prohypertensive and antihypertensive ones, including renin, prostaglandin, kallikrein, other lipid materials, etc.
7. Study the interrelationship of plasma volume, extracellular fluid volume, cardiac output, sodium intake and output and adrenal and other hormones as they relate to the narrowed arterioles encountered in hypertension. Determine why thiazide diuretics, spironlactone and beta-adrenergic blocking drugs decrease arterial pressure.

8. Study the pathophysiology of vascular smooth muscle in hypertension.
9. Determine how hypertension "begets" hypertension; exploration of the "vicious cycle" aspect of hypertension and the means of breaking it.
10. Determine why hypertension leads to an acceleration of atherosclerosis in the cerebral and coronary arteries and why it predisposes to intracerebral hemorrhage.
11. Conduct epidemiological and clinical studies of the genetic, constitutional and environmental factors of importance in hypertension.
12. Determine why hypertension causes changes in the arteriolar wall and the pathophysiologic consequences of these changes. This problem should be studied in diabetes as well as nondiabetic patients.
13. Study the relationship of endogenous mineralocorticoids to hypertension.

1. Determine the etiology and prevention of hypertension. (See 5.4)
2. Improve methods for the diagnosis and long-term treatment of the hypertensive patient. (See 5.4)
3. Develop methods that can be used in the population for the early identification of the stroke-prone individual and especially for a better understanding of the identification, pathogenesis and treatment of transient cerebral ischemia.
4. Investigate the pathophysiological and biochemical changes at the cellular and subcellular level attributable to stroke so that more effective therapeutic measures can be planned.
5. Evaluate the interrelationship of thrombosis and embolization to the atherosclerotic process and the development of stroke and transient ischemic attack. Specific studies to determine the relationship between ulcerated atherosclerotic plaques, embolization and subsequent transient ischemic episodes and stroke, as well as possible development of therapeutic modalities to prevent embolization, should receive high priority. (See Blood Diseases Panel Report)
6. Support scientific evaluation of the best types of acute stroke care and rehabilitation. The determinants of recovery and of successful rehabilitation must be identified. Considering the large sums of money spent for stroke care, the absence of solid scientific evaluation is deplorable. Evaluation of optimal methods of retraining patients both for work and for independent living after stroke are needed.
7. Develop a good animal model of cerebral atherosclerosis and stroke.

1. Promote widespread application of currently available diagnostic and therapeutic methodologies, especially in newborns and infants. This entails improved recognition of the disease through intensive professional education and by development of instrumentation for easy detection; improved interhospital communication and transportation; and making diagnostic and surgical facilities readily available to treat critically ill infant cardiac patients.
2. Investigate the viral, genetic and teratogenic etiology of congenital heart disease as a basis for prevention.
3. Study the basic mechanism of normal and abnormal cardiovascular function in the fetus and the neonate. These studies are essential since the maturing cardiovascular system differs significantly from that of the adult. These studies would form a background for safer and more effective therapy.
4. Determine the natural and unnatural (postoperative) history of congenital heart disease in order to develop improved indications for therapy and later rehabilitation. Serial assessment of function will aid in patient counseling regarding activity levels, career choice, etc. This will provide information for management of the congenital heart disease patient as an adult, identifying anticipated levels of function, determinants of employability, determinants of insurability, etc.
5. Develop further standard surgical therapy and expand to the problem of the neonate and fetus in utero. The application of surgical correction to these populations is necessary if further reduction in the mortality due to congenital heart disease is to be effected.

5.7 RHEUMATIC AND OTHER VALVULAR HEART DISEASES

1. Utilize currently available methods to diagnose, prevent, and treat streptococcal infection, and thus prevent initial and recurrent episodes of rheumatic fever.
2. Utilize currently available methods to diagnose, prevent and treat infective endocarditis.
3. Generate new knowledge about the biologic properties of the streptococcus and the host's immunologic reactions to this organism for application regarding:
 - More rapid, accurate, and inexpensive methods to diagnose streptococcal infection
 - Development of more effective antistreptococcal antibiotics
 - Development of antistreptococcal vaccine.
4. Develop and evaluate noninvasive methods to assess cardiac function in children and adults, and relate the results of cardiac function testing to physical activity and work recommendations, to recommendations for surgical intervention, and to determination of long-term prognosis.
5. Identify risk factors for the development and recurrence of rheumatic fever--both host and organism (streptococcal) factors.
6. Evaluate the behavioral and motivational factors in patient compliance with recommended medical care, as patient education regarding health care and prevention of recurrent disease is a major factor in rehabilitation. Evaluate efficacy of patient and public education programs in influencing these factors.
7. Elucidate the "natural history" of surgically treated chronic rheumatic heart disease with emphasis on restoration of function and on reduction of morbidity and mortality. The data on functional capacity is

needed for rehabilitation efforts which include counseling regarding career or job choice and possible retraining, concerns regarding employability, insurability, etc.

8. Identify the etiologies and incidence of nonrheumatic valvular disease.
9. Identify the incidence and types of cardiovascular complications of drug abuse. Disseminate information to the public regarding the cardiovascular complications of drug abuse and provide professional education regarding their occurrence, diagnosis and management.



1. Identify etiologies of cardiomyopathy by epidemiologic methods, viral and immunologic research, and development and utilization of animal models.
2. Determine the mechanisms of myocardial damage by application of biochemical, biophysiological, physical, and pharmacologic techniques.
3. Identify risk factors predisposing individuals to cardiomyopathy, such as viruses, alcohol, pregnancy, age, malnutrition, stress, immunologic factors, genetic factors, etc.
4. Develop noninvasive techniques to assess myocardial function to aid in the early identification of cardiomyopathy, to delineate the natural history of the disease, and to evaluate therapeutic and rehabilitative intervention.
5. Train physicians to recognize, to systematically identify or classify, and to appropriately treat patients with cardiomyopathy.
6. Develop better (noncardiotoxic) drugs to treat the manifestations of cardiomyopathy. Evaluate current controversial therapeutic approaches, i.e., bedrest, corticosteroid hormones, immunosuppressive agents, etc.
7. Characterize idiopathic hypertrophic subaortic stenosis, a specific form of cardiomyopathy, as to incidence, natural history, etc., to enable evaluation of medical and surgical therapy.



1. Determine the mechanism of generation of cardiac arrhythmias through understanding the normal initiation and propagation of the cardiac impulse and how it is altered in various disease states. This will permit an understanding of how ischemia leads to fatal arrhythmias and allow for the rational design of drugs for the effective prophylaxis and treatment of arrhythmias.
2. Determine specific structural and functional abnormalities of the heart responsible for atrial and ventricular arrhythmias and for heart block.
3. Identify individuals or groups prone to ventricular fibrillation or asystole through epidemiologic studies and provocative tests. This will serve to attack directly the problem of sudden death by identifying the population at risk.
4. Determine whether or not prophylaxis can reduce the incidence of death from cardiac arrhythmias, utilizing either drugs or electronic devices. Selected groups of individuals at risk should be treated with available agents or those to be developed through research to determine whether or not sudden death can be prevented.
5. Develop new drugs for the treatment of arrhythmias and methods to test them through subcellular, cellular, and animal models, and finally in human studies. It is important to devise a rational approach to drug development and design through an understanding of the relationship of chemical structure of a drug to its action as an antiarrhythmic agent.
6. Develop improved bioengineering devices for diagnosis and treatment of arrhythmias. Of particular importance are improved monitoring systems for ambulatory detection of arrhythmias, automatic analysis of the output of these devices, longer-lived and more compact pacemakers and new devices to treat ventricular fibrillation.



7. Educate the public in the recognition and initial management of the life-threatening emergency caused by a sudden arrhythmia.



1. Devise improved methods for the detection, quantification and etiologic diagnosis of cardiac failure in man, both at clinical and cellular levels.
2. Determine the basis, significance and potential reversibility of alterations in cardiac function and abnormalities in cardiac cell growth which accompany heart failure by examining cellular and molecular abnormalities in the hypertrophied and failing heart.
3. Characterize neural, humoral and cellular factors controlling cardiac hemodynamics, the peripheral circulation and body fluid volume, composition and distribution in man. Determine abnormalities in these systems and in organs other than the heart that occur in cardiac failure.
4. Devise better therapy for cardiac failure utilizing the knowledge being developed under recommendations 1 through 3 to extend our ability to utilize existing and to develop new pharmacologic agents.
5. Improve the delivery of care in cardiac failure both by providing more effective therapeutic approaches (above) and through continuing education of physicians and health care personnel, particularly regarding objective assessment of cardiac function and correlation of this with recommendations for activity and for work.
6. Increase the number of trained investigators capable of achieving these significant research goals in the field of cardiac failure.
7. Find better animal models for cardiac failure utilizing both spontaneously occurring animal disease and various induced forms of this condition.

SHOCK

1. Develop a more complete and integrated understanding of the pathophysiological changes and their sequence of development in various forms of shock.
2. Determine the nature and sequence of changes in specific organ functions caused by hypoperfusion.
3. Systematically evaluate the distribution and effects of drugs currently used in the treatment of shock.
4. Develop better models of shock in experimental animals which satisfactorily mimic the human condition. These are essential to recommendations 1 through 3.
5. More widely apply existing methods of hemodynamic and metabolic assessment to treatment and evaluation of patients with shock.
6. Develop and evaluate noninvasive techniques such as ultrasound and isotope studies to evaluate the critical variables in patients with shock and to follow the changes consequent to therapy.
7. Further evaluate available and new devices to assist the circulation and their role in various forms of shock.
8. Determine whether earlier application of available or new forms of treatment will reduce the mortality from shock.
9. Support the training of basic investigators and teams of clinical investigators who will conduct the above studies.
10. Encourage collaborative studies and detailed registries of patients with common forms of shock.



APPENDIX A

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APPENDIX B

PROJECT AREA DISTRIBUTION ANALYSIS



APPENDIX B
PROJECT AREA DISTRIBUTION ANALYSIS

This appendix presents two categories of data displays resulting from analysis of project areas identified by each task group:

- The percentage distribution of project areas with respect to the 10 legislative requirements
- The percentage distribution of project areas with respect to the four program objectives.

These results were obtained by a subjective comparison of each project area against the legislation requirements and objectives. These distributions do not reflect the relative manpower or funding required in any objective or legislative category since they are based only on the number of project areas identified.



1. Distribution of Project Areas with Respect to the Legislation

Table B-1 presents, on a task group basis, the percentage of project areas which relate to specific legislative planning requirements. The percentage distribution for all the task groups as a composite is shown in Figure B-1, and Figure B-2 presents the percentage distribution for each task group.

The 10 legislative requirements are as follows:

"... (1) investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;

"(2) studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena;

"(3) research into the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases;

"(4) establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases;



"(5) establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases;

"(6) studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products;

"(7) the education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases;

"(8) public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources;

"(9) establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases; and

"(10) establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services..."



Table B-1
DISTRIBUTION OF PROJECT AREAS
WITH RESPECT TO THE LEGISLATIVE REQUIREMENTS

Task Group	No. of Project Areas	Legislative Requirement									
		1	2	3	4	5	6	7	8	9	10
Atherosclerosis	128	65%	28%	4%	11%	43%	0	0	15%	0	12%
Coronary Heart Disease	93	72%	60%	22%	21%	55%	0	6%	18%	0	14%
Peripheral Vascular Disease	23	26%	52%	43%	22%	35%	13%	61%	39%	13%	35%
Hypertension	63	49%	65%	46%	17%	59%	0	0	11%	3%	8%
Stroke	70	37%	57%	69%	61%	44%	0	0	6%	0	0
Congenital Heart Disease	48	67%	69%	63%	50%	63%	0	19%	4%	100%	13%
Rheumatic and Other Valvular Heart Diseases	52	64%	50%	40%	37%	69%	0	23%	33%	92%	23%
Cardiomyopathy	129	69%	78%	37%	31%	37%	0	0	2%	1%	7%
Arrhythmia	62	60%	69%	73%	58%	63%	0	27%	2%	3%	3%
Cardiac Failure	119	39%	93%	96%	61%	94%	1%	93%	6%	100%	10%
Shock	66	88%	38%	13%	29%	23%	0	0	3%	0	1%
TOTAL	853	63%	62%	45%	36%	55%	1%	20%	11%	27%	10%

Figure B-1

COMPOSITE FOR ALL TASK GROUPS

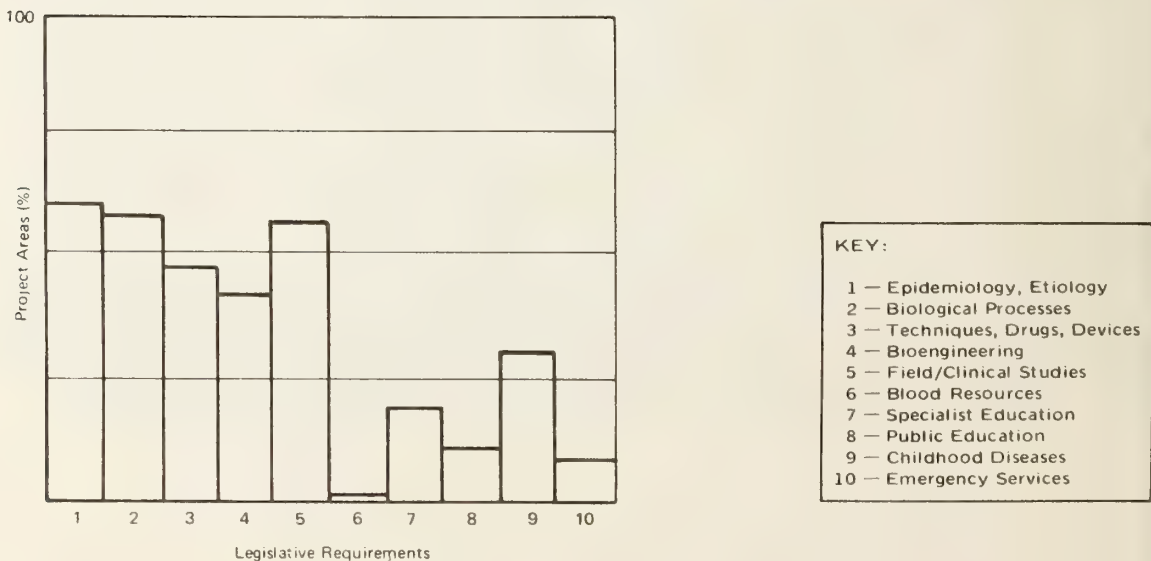


Figure B-2
INDIVIDUAL TASK GROUPS

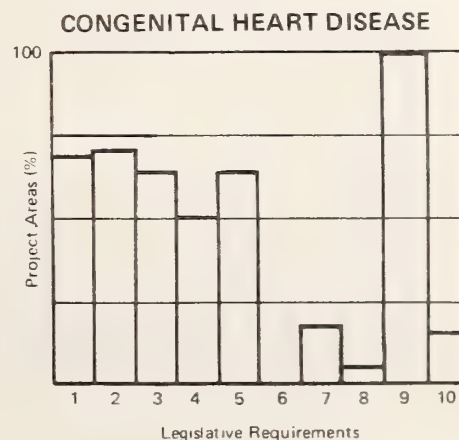
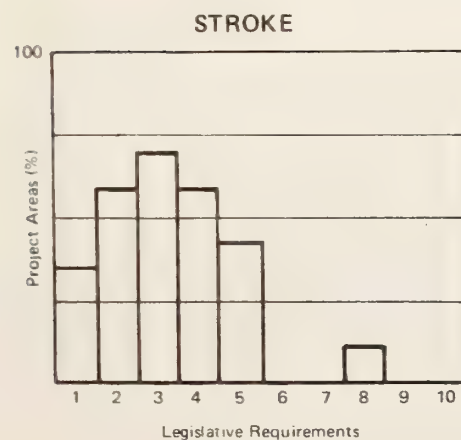
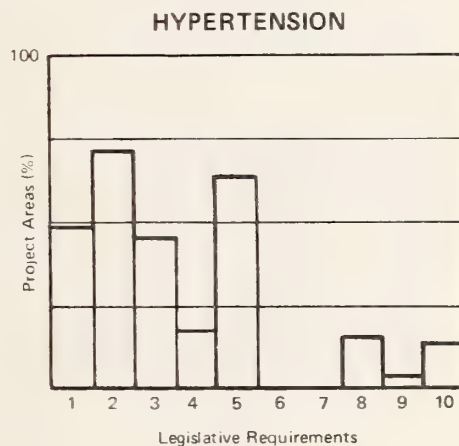
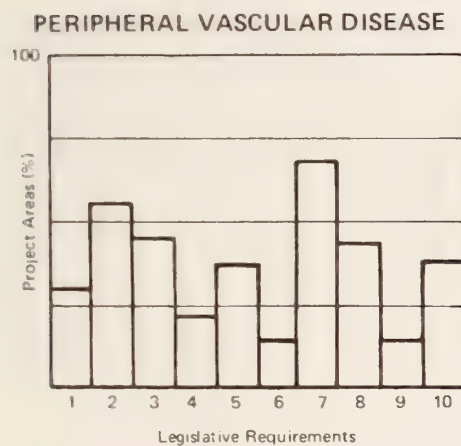
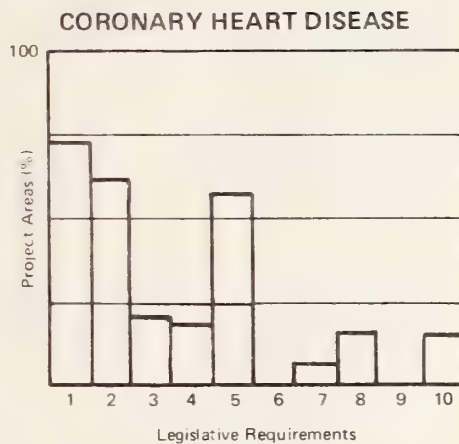
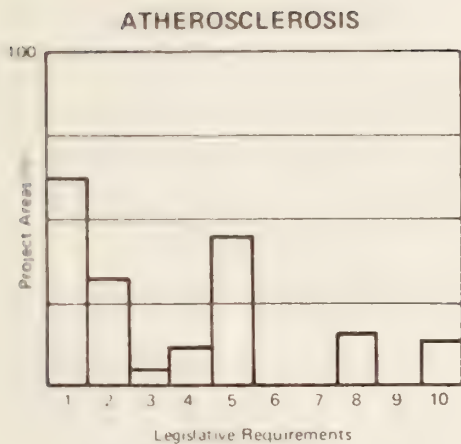


Figure B-2
INDIVIDUAL TASK GROUPS (continued)



2. Distribution of Project Areas with Respect to the Program Objectives

Table B-2 presents, on a task group basis, the percentage of project areas which relate to the four primary program objectives. The percentage distribution for all the task groups as a composite is shown in Figure B-3, and Figure B-4 presents the percentage distribution for each task group.

The four primary program objectives are:

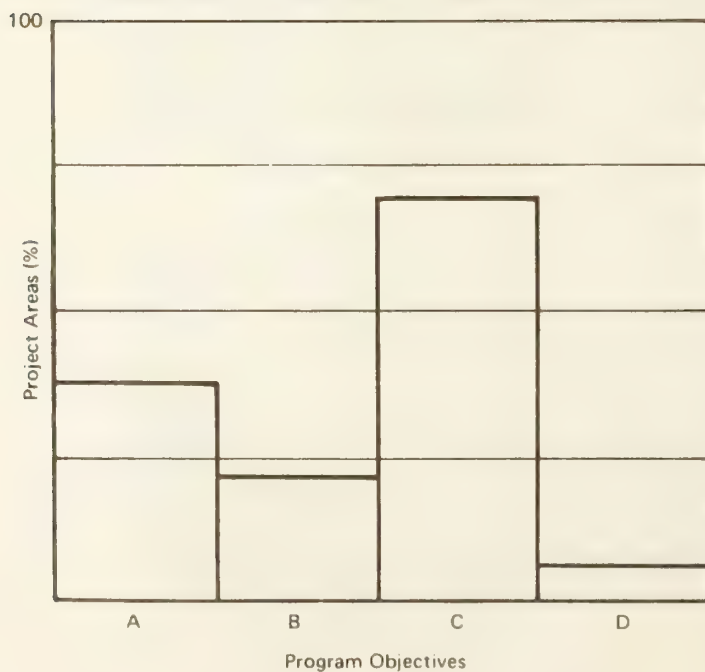
- A. Prevention
- B. Detection and Diagnosis
- C. Treatment and Management
- D. Rehabilitation.



Table B-2
DISTRIBUTION OF PROJECT AREAS WITH RESPECT
TO THE PROGRAM OBJECTIVES

Task Group	No. of Project Areas	Primary Program Objectives			
		A	B	C	D
Atherosclerosis	128	65%	9%	68%	1%
Coronary Heart Disease	93	40%	13%	77%	4%
Peripheral Vascular Disease	23	35%	30%	65%	9%
Hypertension	63	35%	32%	97%	0
Stroke	70	27%	41%	34%	11%
Congenital Heart Disease	48	58%	15%	27%	17%
Rheumatic and Other Valvular Heart Diseases	52	50%	32%	46%	11%
Cardiomyopathy	129	51%	29%	42%	7%
Arrhythmia	62	34%	18%	71%	0
Cardiac Failure	119	7%	12%	92%	1%
Shock	66	3%	6%	99%	0
TOTAL	853	37%	20%	67%	5%

Figure B-3
COMPOSITE FOR ALL TASK GROUPS



KEY:

- A – Prevention
- B – Detection and Diagnosis
- C – Treatment and Management
- D – Rehabilitation

Figure B-4
INDIVIDUAL TASK GROUPS

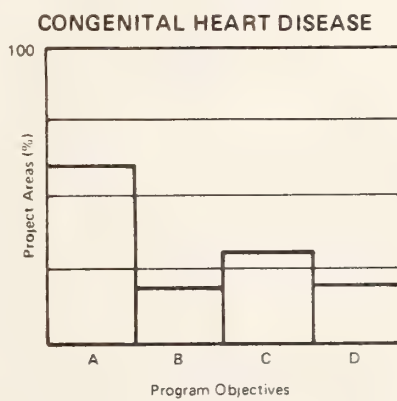
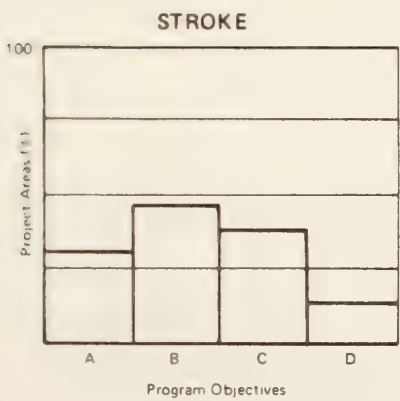
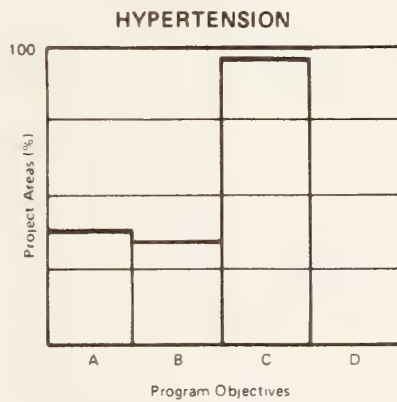
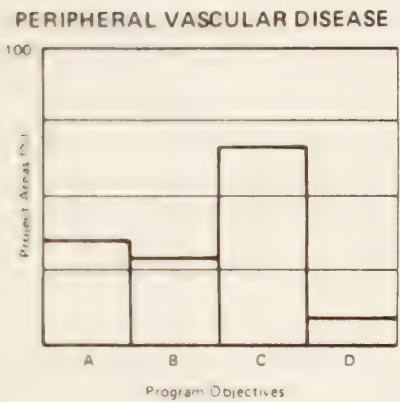
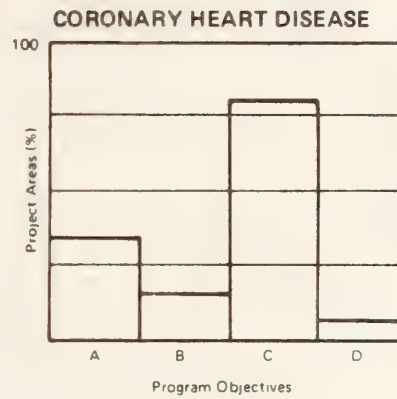
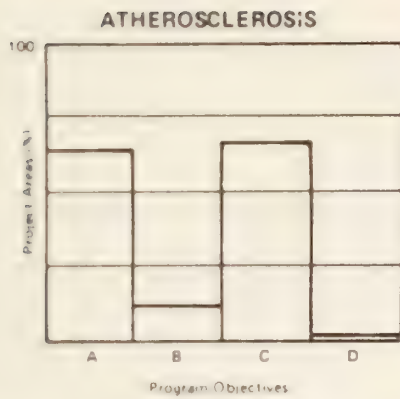
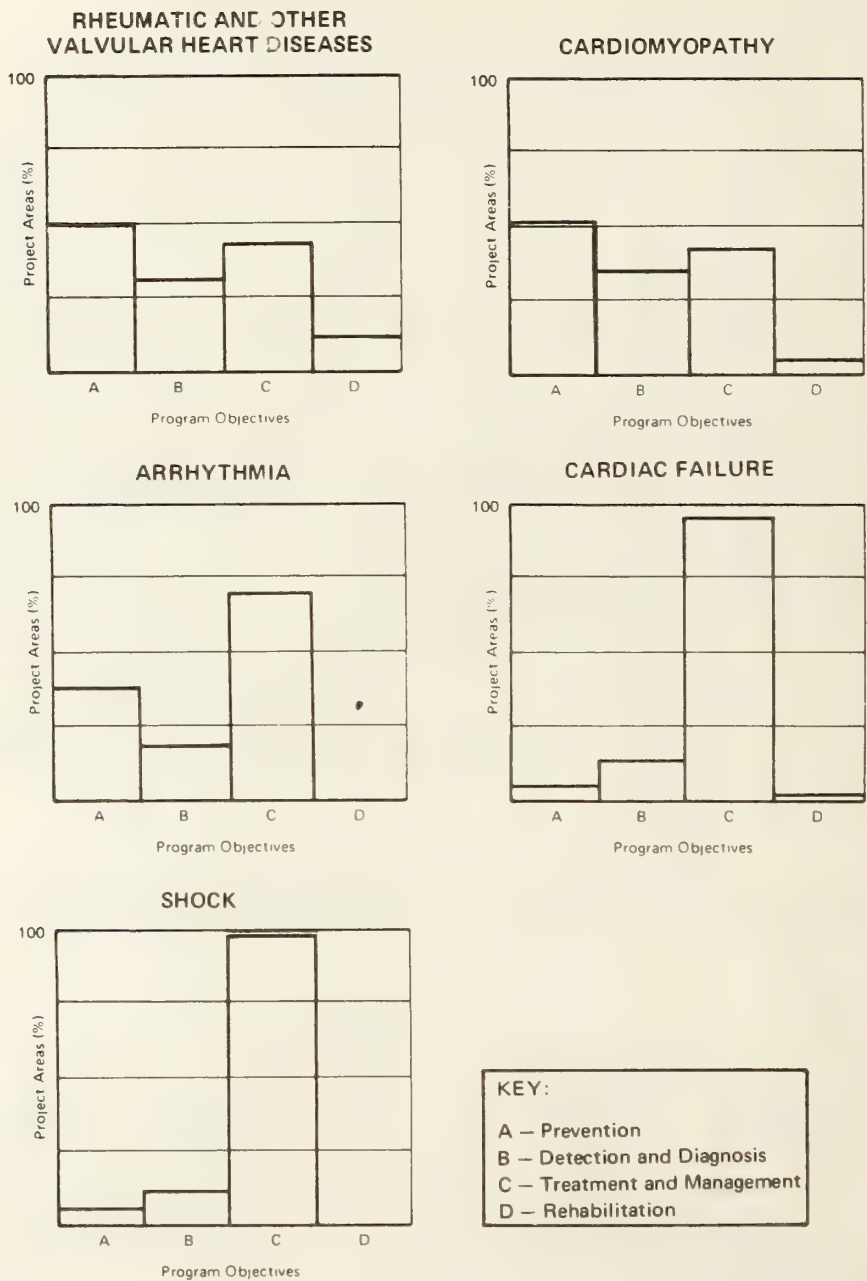


Figure B-4
INDIVIDUAL TASK GROUPS (continued)



APPENDIX C

DATA SUMMARY



APPENDIX C
DATA SUMMARY

This appendix provides a summary of the data base, i.e., the problems, approaches and project areas, which resulted from extensive deliberations of the 11 Task Groups. A detailed discussion of each of these items is given in the individual Task Group materials.

The numbers of problems, approaches, and project areas identified by each Task Group are summarized in Table C-1. The listing which follows provides the corresponding titles for each category, ordered by number. The first digit identifies the problem, the second digit the approach, and the third digit the project area.

Table C-1

DATA SUMMARY FOR HEART AND BLOOD VESSEL DISEASES PANEL

No.	Task Group	Problems	Approaches	Project Areas
1	Atherosclerosis	8	33	128
2	Coronary Heart Disease	1	15	93
3	Peripheral Vascular Disease	1	4	23
4	Hypertension	1	3	63
5	Stroke	1	3	70
6	Congenital Heart Disease	1	11	48
7	Rheumatic and Other Valvular Heart Diseases	1	11	52
8	Cardiomyopathy	1	26	129
9	Arrhythmia	4	11	62
10	Cardiac Failure	3	19	119
11	Shock	2	20	66
TOTAL		24	156	853

DATA SUMMARY FOR
TASK GROUP 1

ATHEROSCLEROSIS



PROBLEM 1. HYPERLIPIDEMIA

- 1.1 Environmental and Behavioral Effects on Serum Lipids.
 - 1.1.1 Identify hyperlipidemic groups.
 - 1.1.2 Psychosocial effects on serum lipids.
 - 1.1.3 Effect of cigarette smoking and physical exertion on serum lipids.
 - 1.1.4 Effects of intestinal flora on serum lipids.
 - 1.1.5 Mechanisms of psychosocial stress on serum lipids.
 - 1.1.6 Search for other physical and biological factors affecting serum lipids.
- 1.2 Regulation of Plasma Lipoprotein Concentrations.
 - 1.2.1 Biosynthesis and secretion of lipoproteins.
 - 1.2.2 Intravascular changes in and interconversions of lipoproteins.
 - 1.2.3 Characterization of enzymes acting on lipoproteins.
 - 1.2.4 Factors regulating removal of lipoproteins from plasma.
 - 1.2.5 Sites and mechanisms of removal of lipoproteins from plasma.
 - 1.2.6 Mechanism of genetically determined hyperlipoproteinemia.
- 1.3 Role of Serum Lipids in Pathogenesis of Atherosclerosis.
 - 1.3.1 Develop methods to identify lipids and lipoproteins in tissues.
 - 1.3.2 Determine nature and source of abnormal lipid deposits in human and in experimental animal lesions.
 - 1.3.3 Effect of altering serum lipids on established atherosclerotic lesions in experimental animals.
 - 1.3.4 Interaction of lipoprotein and lipids with arterial intima.
- 1.4 Dietary Effects on Hyperlipidemia.
 - 1.4.1 Role of dietary fat, cholesterol, carbohydrate, and other factors in hyperlipidemia.
 - 1.4.2 Biochemical mechanisms by which dietary factors control serum lipoproteins.
 - 1.4.3 Effects of dietary modifications on atherosclerosis.
 - 1.4.4 Animal models for studying dietary modifications.
 - 1.4.5 Other dietary factors affecting serum lipids.
 - 1.4.6 Potential adverse effects of diets that lower serum lipids.
- 1.5 Dietary Modifications to Lower Blood Cholesterol Level.
 - 1.5.1 Determine the cholesterol and fatty acid composition of food.
 - 1.5.2 Produce, by selective breeding or feeding, butter fat, eggs, and beef low in cholesterol and saturated fat.
 - 1.5.3 Reduce the level of saturated fat and cholesterol in butter fat, eggs, and beef by manufacturing processes.
 - 1.5.4 Reduce the absorbability of saturated fatty acids and cholesterol in butter fat, eggs, and beef.
 - 1.5.5 Develop acceptable replacements for eggs, butter fat, and beef.
 - 1.5.6 Social and cultural factors affecting diet.

- 1.5.7 Means to educate the hyperlipidemic.
- 1.5.8 Motivation of high-risk individuals to follow proper diet.
- 1.5.9 Professional education for dietary control of hyperlipidemia.
- 1.6 Hyperlipidemia in the General Population.
 - 1.6.1 Simple method for detecting hypertriglyceridemia.
 - 1.6.2 Detection and referral system for hyperlipidemia.
 - 1.6.3 Dietary instructional resources.
 - 1.6.4 Psychological reinforcement for dietary adherence.
- 1.7 Lipid Metabolism.
 - 1.7.1 Intermediates in lipid metabolism.
 - 1.7.2 Enzymatic mechanisms in lipid synthesis and breakdown.
 - 1.7.3 Hormonal influences on lipid metabolism.
 - 1.7.4 Interrelationships between lipid metabolism and metabolism of lipoprotein apoproteins.
- 1.8 Blood Lipid and Lipoprotein Regulation.
 - 1.8.1 Mechanisms of transfer of lipids between blood and tissues.
 - 1.8.2 Interspecies differences in lipid partition between blood and tissues.
 - 1.8.3 Hormonal effects on blood lipid concentrations.
- 1.9 Clarification of Genetics of Hyperlipidemia in Man.
 - 1.9.1 Develop improved system of genetic classification of hyperlipidemia.
 - 1.9.2 Develop specific biochemical genetic markers.
 - 1.9.3 Genetic linkages for hyperlipidemias.
 - 1.9.4 Determine formal genetics and population frequency of inherited hyperlipidemias.
 - 1.9.5 Natural history of genetic and nongenetic hyperlipidemia.
 - 1.9.6 Methods of genetic counseling to families with hyperlipidemia.
 - 1.9.7 Animal models with genetic hyperlipidemia.
- 1.10 Chemistry of the Lipoproteins.
 - 1.10.1 Characterize normal human plasma lipoproteins.
 - 1.10.2 Characterize normal plasma lipoproteins in animals.
 - 1.10.3 Lipid-apoprotein interactions.
 - 1.10.4 Characterize lipoprotein apoproteins as to primary, secondary, and tertiary structure.
 - 1.10.5 Lipoproteins in hyperlipoproteinemias.
- 1.11 Development of Hypolipidemic Agents.
 - 1.11.1 Establish methods for efficient screening of hypolipidemic agents.
 - 1.11.2 Test known chemicals for effects of lipid metabolism.
 - 1.11.3 Synthesize new compounds for control of lipid metabolism.
 - 1.11.4 Test promising agents for lipid-lowering effectiveness in animals.
 - 1.11.5 Test effective agents for toxicity in animals.

- 1.11.6 Test new agents for lipid-lowering in human subjects.
- 1.11.7 Test proven lipid-lowering agents for prevention of atherosclerosis.
- 1.12 Effects of Commonly Used Drugs on Blood Lipids.
 - 1.12.1 Test drugs for effects on blood lipids in experimental animals.
 - 1.12.2 Survey populations receiving drugs for blood lipid levels.

PROBLEM 2. BEHAVIOR

- 2.1 Psychological and Social Influences on Atherosclerosis.
 - 2.1.1 Social factors affecting atherosclerosis.
 - 2.1.2 Individual behavioral factors affecting atherosclerosis.
 - 2.1.3 Childhood and early adult behavioral characteristics predictive of atherosclerotic disease.
 - 2.1.4 Interactions of social and behavioral variables.
 - 2.1.5 Genetic determinants of behavioral factors.
- 2.2 Biological Mechanisms by Which Behavior Influences Atherosclerosis.
 - 2.2.1 Behavioral factors in animal models.
 - 2.2.2 Biological responses in persons undergoing stress.
 - 2.2.3 Clinical disorders of the behavior-atherosclerosis linkage.
 - 2.2.4 Behavior modification affects on atherosclerosis.
- 2.3 Assess Behaviors Affecting Exposure to Environmental Agents.
 - 2.3.1 Develop measures of cigarette smoking.
 - 2.3.2 Develop measures of food intake.
 - 2.3.3 Develop measures of adherence to prescribed medications.
- 2.4 Modification of Personal Health Maintenance Practices.
 - 2.4.1 Develop methods of altering behavior.
 - 2.4.2 Measure effectiveness of current and new practices to achieve desired habits.
 - 2.4.3 Improve skills of health care personnel in inducing behavior changes.

PROBLEM 3. TISSUE PATHOGENESIS

- 3.1 Definition of Arterial Growth, Structure, Function and Metabolism.
 - 3.1.1 Cytokinetics of vessel development; intercellular interactions; and production of intercellular substances.
 - 3.1.2 Energy requirements of the vessel and metabolic processes normal to the vessel during growth and function.
 - 3.1.3 Maintenance of vascular integrity; aging and regressive changes.
- 3.2 Biochemical, Structural and Functional Development of Lesions.
 - 3.2.1 Vascular injuries.
 - 3.2.2 Repair of vascular injury.
 - 3.2.3 Plaque evolution.

- 3.3 Interaction of Vessel Wall with Circulating Blood.
 - 3.3.1 Interaction with lipoproteins by type and concentration.
 - 3.3.2 Interaction with hemostatic elements.
 - 3.3.3 Inflammatory and immunopathological phenomena.
 - 3.3.4 Hemodynamic phenomena in atherosclerosis.
- 3.4 Genetic Characteristics of Vessel Wall in Respect to Atherogenesis.
 - 3.4.1 Identification of animal models that can be selectively bred for differences in plaque pathogenesis.
 - 3.4.2 Comparative studies of local arterial structure, metabolism, cellular kinetics and production of intercellular materials in genetically distinct models.
- 3.5 Studies on Plaque Regression.
 - 3.5.1 Biochemical and structural correlative studies of early and of chronic plaques at various stages of regressive evolution.
 - 3.5.2 Ascertainment of plaque regression in man.
 - 3.5.3 Ascertainment of the limitations of regression towards normal.
 - 3.5.4 Ascertainment and elucidation of functional in contrast to structural regression.

PROBLEM 4. SMOKING

- 4.1 Legislation to Suppress or Reduce Cigarette Smoking.
 - 4.1.1 Reduction of subsidies to tobacco producers.
 - 4.1.2 Tax benefits to noncigarette smokers.
 - 4.1.3 Bans on cigarette advertising.
 - 4.1.4 Anticigarette smoking media campaign.
- 4.2 Alteration of Public Habits.
 - 4.2.1 Media campaigns to reduce smoking.
 - 4.2.2 School campaigns to keep young people from smoking.
 - 4.2.3 Financial incentives for not smoking cigarettes.
 - 4.2.4 Etiology of cigarette smoking.
- 4.3 Modify Physician and Health Professional Behavior in Relation to Cigarette Smoking.
 - 4.3.1 Develop education programs for health professionals.
- 4.4 Eliminate Atherogenic Effect of Cigarette Smoking.
 - 4.4.1 Effect of cigarette smoking in humans on other known risk factors and on intermediary mechanisms of atherosclerosis.
 - 4.4.2 Develop nonhuman primate models of cigarette smoking that simulate chronic heavy cigarette smoking in humans.
 - 4.4.3 Develop safe cigarettes or a protective regimen for the smoker.

PROBLEM 5. BLOOD PRESSURE (SEE HYPERTENSION REPORT)

PROBLEM 6. DIABETES MELLITUS

- 6.1 Determine Mechanism by Which Impaired Glucose Tolerance Aggravates Atherosclerosis.
 - 6.1.1 Develop in vivo animal models for studying effect of diabetes mellitus on pathogenesis of atherosclerosis.
 - 6.1.2 Develop in vitro human models for studying arterial wall metabolism.
 - 6.1.3 Determine genetic interrelationships involving diabetes mellitus, hypertriglyceridemia, and atherosclerosis.
- 6.2 Protection of Diabetics from Atherosclerosis.
 - 6.2.1 Nonatherogenic diets for diabetics.
 - 6.2.2 Drugs for diabetics and atherosclerosis.

PROBLEM 7. HEMOSTASIS

- 7.1 Hemostatic Mechanism in Pathogenesis of Atherosclerosis.
 - 7.1.1 Identification of the "hypercoagulable" state.
 - 7.1.2 Effect of atherogenic diets on hemostatic mechanism.
 - 7.1.3 Hemostatic components in atherosclerotic lesions.
 - 7.1.4 Interactions between risk factors, atherosclerosis, and hemostatic mechanism.
 - 7.1.5 Retard atherosclerosis by altering hemostatic mechanism.

PROBLEM 8. OTHER AGENTS AFFECTING ATHEROSCLEROSIS

- 8.1 Sex and Hormone Effects on Atherosclerosis.
 - 8.1.1 Hormonal and metabolic responses to atherogenic agents by sex.
 - 8.1.2 Differential responses of male and female twins to atherogenic challenges.
- 8.2 Blood Groups and Atherosclerosis.
 - 8.2.1 Association of blood groups with susceptibility to atherosclerosis in animals.
 - 8.2.2 Blood markers and susceptibility to atherosclerosis in animals.
- 8.3 Hyperuricemia and Atherosclerosis.
 - 8.3.1 Hyperuricemia as a risk factor in atherosclerosis.
 - 8.3.2 Effect of reducing hyperuricemia on frequency of atherosclerotic disease.
- 8.4 Trace Substances and Atherosclerosis.
 - 8.4.1 Relation of trace elements to atherosclerosis in autopsy populations.
 - 8.4.2 Effect on animal models of intake of trace substances.
 - 8.4.3 Refine methodology for laboratory measurements of trace substances in tissues.
 - 8.4.4 Epidemiological studies of trace substances in relation to atherosclerotic diseases.
- 8.5 Hematocrit Effects on Atherosclerosis.
 - 8.5.1 Effect of hematocrit on experimental atherosclerosis.
 - 8.5.2 Effect of hematocrit on human atherosclerosis.

DATA SUMMARY FOR
TASK GROUP 2

CORONARY HEART DISEASE

PROBLEM 1. CORONARY HEART DISEASE

- 1.1 Definition, Classification and Categorization of Syndromes.
 - 1.1.1 A series of conferences to review existing experience and develop a standardized system of nomenclature.
 - 1.1.2 Develop a standard system for the recording of the results of coronary arteriography and ventriculography.
 - 1.1.3 Develop a standard system for the interpretation and recording of the results of exercise testing.
 - 1.1.4 Prospective studies of coronary heart disease in the U.S.A. and in countries in which surgical therapy is less popular than in U.S.A.
- 1.2 Epidemiology, Natural History and Prognosis.
 - 1.2.1 Collection and validation of data on clinically inapparent heart disease.
 - 1.2.2 Identification of patients with risk factors prone to develop coronary heart disease.
 - 1.2.3 Development of new techniques for the detection, quantification and follow-up of patients.
 - 1.2.4 Determination of factors responsible for the change in clinical course or progression of coronary heart disease.
- 1.3 Factors Precipitating Acute Myocardial Ischemia, Infarction and Related Syndromes.
 - 1.3.1 Pathoanatomical aspects of coronary circulation in production of ischemic injury.
 - 1.3.2 Pathophysiological aspects of coronary circulation in production of ischemic injury.
 - 1.3.3 Intravascular factors in production of ischemic injury.
 - 1.3.4 Nonvascular factors in production of ischemic injury.
- 1.4 The Effect of Ischemia on the Heart at Both Cellular and Organ Level.
 - 1.4.1 Experimental methods for achieving and assessing a controlled degree and extent of ischemia and/or infarction.
 - 1.4.2 Interrelation of restricted blood flow and myocardial metabolic and mechanical activity.
 - 1.4.3 Effects of stages of ischemic injury on myocellular function.
 - 1.4.4 Electrophysiologic consequences of ischemic injury.
 - 1.4.5 Mechanical consequences of ischemic injury.
 - 1.4.6 Symptomatic consequences of ischemic injury.
- 1.5 The Development of Methods, Procedures and Population Risk Data for Minimizing Sudden Deaths.
 - 1.5.1 Precipitating, trigger and pathophysiological mechanisms of sudden cardiac death.
 - 1.5.2 The role of preexisting disease.
 - 1.5.3 Better defined risk factors and more sensitive premonitory signs of sudden cardiac death.
 - 1.5.4 Recognition and quantification of occult coronary heart disease.
 - 1.5.5 Make coronary angiography simpler and more readily available.
 - 1.5.6 Reduction in coronary arteriosclerosis.

- 1.5.7 Chronic prophylactic antiarrhythmic regimens.
- 1.5.8 Intermittent prophylactic antiarrhythmic regimens.
- 1.5.9 Early administration of antiarrhythmic agents upon symptoms of apparent heart attack.
- 1.5.10 Surgical techniques for bypassing coronary arteriosclerotic lesions.
- 1.5.11 Diminishing metabolic requirements of the heart.
- 1.5.12 Devices for influencing the heart rate, rhythm, and workload of the heart.
- 1.5.13 Basic research in electrophysiology, myocardial metabolism, drug metabolism, and electromechanical interactions.
- 1.5.14 Education and emergency care systems.
- 1.6 Detection and Quantification of Coronary Atherosclerosis, Myocardial Ischemia and Myocardial Infarction.
 - 1.6.1 Evaluate present techniques and develop new methods for determining quantitatively electrical abnormalities.
 - 1.6.2 Evaluate and improve existing, and develop new angiographic techniques for quantitating abnormalities in coronary blood flow.
 - 1.6.3 Improve presently available nonangiographic techniques for determining anatomy of coronary vessels, flow patterns and flow distribution and where possible devise noninvasive techniques.
 - 1.6.4 Develop methods for quantifying areas of ischemia and infarction.
 - 1.6.5 Improve available methods for determining mechanical abnormalities and develop and validate new quantitative noninvasive methods.
- 1.7 Development of General Principles for Study Designs of Therapy.
 - 1.7.1 Principles of study design.
 - 1.7.2 Biomathematical critiques of discriminatory powers of test.
- 1.8 Surgical Therapy of Myocardial Ischemia.
 - 1.8.1 Prospective randomized studies comparing the medical and surgical management of critical obstruction of a single coronary in patients with normal ventricular function.
 - 1.8.2 Randomized study comparing the surgical and medical management of asymptomatic survivors of their first myocardial infarction who had no angina prior to their first infarction.
 - 1.8.3 Randomized study of the group of patients with unstable angina.
 - 1.8.4 Randomized study comparing the medical and surgical management of acute myocardial infarction seen within the first few hours in patients presenting with heart failure or shock.
 - 1.8.5 Randomized study of patients with significant left ventricular dysfunction as the predominant symptom rather than angina.
 - 1.8.6 Randomized study of patients with stable mild angina.
 - 1.8.7 Randomized prospective study of the effects of bypass surgery on "critical" obstruction of coronary arteries.
 - 1.8.8 Randomized prospective study of the effect of surgical bypass on noncritical obstructive coronary lesions.

- 1.8.9 Randomized prospective study of patients who have been asymptomatic but who underwent angiography as a result of normal electrocardiogram or exercise response who were found to have abnormal anatomy of the coronary vessels.
- 1.8.10 Prospective studies for the development of an animal model to provide a basis for studying various medical and therapeutic regimens for atherosclerosis.
- 1.8.11 Randomized studies on animal models for the feasibility of surgical treatment for acute myocardial infarction.
- 1.8.12 Trial therapy for the prospective methods of minimizing the consequences of ischemia or infarction in animal models.
- 1.8.13 Retrospective studies of the effect of bypass operations on the native coronary circulation in vessels with critical obstruction.
- 1.8.14 Retrospective studies of the effect of bypass on the native coronary circulation in vessels with noncritical obstruction.
- 1.8.15 Retrospective studies in patients with significant left ventricular dysfunction as their prominent symptoms rather than angina.
- 1.8.16 Retrospective study of patients who required defibrillation or pacing in coronary care unit following myocardial infarction who were resuscitated and later underwent coronary catheterization to characterize the anatomic characteristics of patients who fibrillate.

1.9 Therapeutics: Medical Therapy in Myocardial Ischemia.

- 1.9.1 Studies in interventions influencing myocardial blood flow (i.e., enhance myocardial oxygen delivery).
- 1.9.2 Studies of interventions influencing cardiac work (mechanical performance): (a) B-adrenergic blocking agents, (b) inotropic agents, (c) diuretics, (d) other, e.g., stimulating carotid sinus mechanical assist.
- 1.9.3 Studies of interventions to alter risk factors: (a) psychological-personality, (b) lipid, (c) smoking, (d) exercise status, (e) obesity, etc.
- 1.9.4 Studies to evaluate interventions in unstable angina: (a) drugs, (b) mechanical devices.
- 1.9.5 Studies to evaluate interventions in heart failure.

1.10 Therapeutics: Minimizing the Consequences of Myocardial Infarction.

- 1.10.1 Alteration of hemodynamics: (a) mechanical, (b) pharmacological.
- 1.10.2 Modification of metabolic and biochemical factors.
- 1.10.3 Drug interventions which may influence vessel wall responses, including clotting considerations.
- 1.10.4 Prospective studies to establish the angiographic, anatomic, and direct observation characteristics of ischemic coronary disease associated with papillary muscle dysfunction as a cause of mitral insufficiency and cardiac failure.
- 1.10.5 Prospective studies of surgical therapy of ventricular septal defect complicating myocardial infarction.

Control and treatment of arrhythmias occurring as a consequence of myocardial infarction is covered by Arrhythmia, Task Group No. 9.

Treatment of congestive failure as a consequence of myocardial infarction is covered by Cardiac Failure, Task Group No. 10.

Treatment of shock as a consequence of myocardial infarction is covered by Shock, Task Group No. 11.

- 1.11 Methods of Preventive Cardiology.
 - 1.11.1 Community approaches to screening, testing, registration and follow-up for disease prevention.
 - 1.11.2 Applied exercise cardiology networks.

Alterations in life style, patient education, and psychodynamics of denial and motivation are dealt with in 1.5 and 1.9.
- 1.12 Cardiac Transplantation.
 - 1.12.1 Investigation of improved donor-recipient identification and availability.
 - 1.12.2 Improve methods of detecting and preventing acute rejection.
 - 1.12.3 To use human allografts and primate models of allografts to develop a better understanding of coronary atherosclerosis.
 - 1.12.4 To determine the functional characteristics of the denervated transplanted heart.
 - 1.12.5 To develop new approaches for cardiac replacement.
- 1.13 Cardiac Replacement with an Artificial Heart.
 - 1.13.1 Development of energy systems.
 - 1.13.2 Biomaterials development.
 - 1.13.3 Control systems development.
 - 1.13.4 Development of entire system.
 - 1.13.5 Long-term performance testing in large animals.
- 1.14 Improved Methods for Providing Emergency Services.
 - 1.14.1 Analysis and solutions of community problems responsible for delay in initiating coronary care.
 - 1.14.2 Design and evaluate systems to shorten delays in initiating coronary care in urban, suburban and rural communities.
 - 1.14.3 Designing of improved methods of communication between patient and physician or hospital with immediate response capability.
 - 1.14.4 Establishing systems and methods of transportation.
 - 1.14.5 Establishing community-wide referral centers for acute coronary care.
 - 1.14.6 Establishing training programs and appropriate legislation for paramedical persons engaged in out-of-hospital coronary care, especially in cardiopulmonary resuscitation; administration of drugs, electrical defibrillation, and EKG reading of arrhythmia.
 - 1.14.7 Improving the technique of cardiopulmonary resuscitation.
 - 1.14.8 Improving arrhythmia control.
 - 1.14.9 Identification of the population of high risk to acute coronary insufficiency or sudden death.
- 1.15 Rehabilitation.
 - 1.15.1 Basic research into components of rehabilitative processes.
 - 1.15.2 Demonstrative units for clinical application and training.
 - 1.15.3 Role of government agencies, industrial labor unions and the insurance industry.

DATA SUMMARY FOR
TASK GROUP 3

PERIPHERAL VASCULAR DISEASE



PROBLEM 1. PERIPHERAL VASCULAR DISEASE

- 1.1 Quantitation of Peripheral Vascular Disease.
 - 1.1.1 Development of methods to accurately quantitate peripheral blood flow.
 - 1.1.2 Development of noninvasive techniques to determine size and sites of vascular obstruction.
 - 1.1.3 Serum factors or enzyme levels correlating with degree of obstructive disease.
 - 1.1.4 Model programs for mass screening of patients with susceptible age ranges—standardize criteria.
 - 1.1.5 Training of health team regarding detection using modern methods.
 - 1.1.6 Education of lay public regarding risk factors.
- 1.2 Therapeutic Approach to Peripheral Vascular Disease.
 - 1.2.1 Methods to increase collateral blood flow.
 - 1.2.2 Prosthetic arterial substitutes.
 - 1.2.3 Studies regarding anticoagulants, blood viscosity, platelet aggregations.
 - 1.2.4 Training of medical specialists in vascular disease.
 - 1.2.5 Methods to quantitate peripheral blood flow (noninvasive).
 - 1.2.6 Evaluation of medications to reverse primary disease process.
 - 1.2.7 Methods of increasing flow through diseased vessels—drugs, A.V. shunts.
 - 1.2.8 Studies of vessel wall relation to blood elements regarding sheering stress.
- 1.3 Alleviation of Disability from Peripheral Vascular Disease.
 - 1.3.1 Program to establish criteria for type of therapy, direct surgery, medications, amputation.
 - 1.3.2 Rehabilitation programs—medical and employment.
 - 1.3.3 Job retraining to limit walking or standing.
- 1.4 Elimination or Reduction of Peripheral Vascular Disease.
 - 1.4.1 Investigate the basic mechanism of the role of diabetes, insulin, hyperglycemia of the arterial system.
 - 1.4.2 Understand the role of smoking in acceleration of the process.
 - 1.4.3 Evaluate effects of marijuana on peripheral vascular system.
 - 1.4.4 Studies on the metabolic and functional state of the arterial wall.
 - 1.4.5 Control or prevention of atherosclerosis.
 - 1.4.6 Education of professionals to assist the public in avoiding risk factors and in better control of associate illnesses. The development of vascular specialists via continuing education, emphasis on nutrition and medical school inputs.

DATA SUMMARY FOR
TASK GROUP 4

HYPERTENSION



PROBLEM 1. HYPERTENSION

- 1.1 Mechanisms, Characteristics and Epidemiology of Hypertension.
 - 1.1.1 Role of aldosterone and other mineralocorticoids in hypertension.
 - 1.1.2 Renal perfusion pressure, intrarenal pressure and exaggerated natriuresis in hypertension.
 - 1.1.3 Plasma and ECF volumes in hypertension.
 - 1.1.4 Renin and angiotensin in the causation of hypertension and as a causal factor in its consequences.
 - 1.1.5 Determine the role of prostaglandins in hypertension.
 - 1.1.6 Role of kallikrein and Bradykinin in hypertension.
 - 1.1.7 Role of other endogenous pro- and antihypertensive substances in hypertension.
 - 1.1.8 Determinants of resting blood pressure (normal and abnormal).
 - 1.1.9 Autonomic nervous system and brain stem reflexes in the control of blood pressure.
 - 1.1.10 The hypothalamus in higher centers.
 - 1.1.11 Dietary factors in hypertension.
 - 1.1.12 What is the relationship of obesity to hypertension?
 - 1.1.13 The relationship of the kidneys to hypertension.
 - 1.1.14 The "vicious cycle" in hypertension and means for breaking it.
 - 1.1.15 Basic physiology of vascular smooth muscle.
 - 1.1.16 Renal blood flow and hypertension.
 - 1.1.17 Innervation of the kidney in hypertension.
 - 1.1.18 Cardiac output in young hypertensives.
 - 1.1.19 Effect of socio-economic factors on hypertension.
 - 1.1.20 Genetic factors in hypertension. (Why do Blacks suffer more?)
 - 1.1.21 Why and how does bedrest lower blood pressure?
 - 1.1.22 Drug-induced hypertension.
 - 1.1.23 Role of adrenal cortex in high blood pressure: pharmacologic.
 - 1.1.24 Toxemia of pregnancy and its relationship to hypertension.
 - 1.1.25 Role of psychological factors in hypertension.
 - 1.1.26 Determination of the role of menopause in precipitating hypertension.
 - 1.1.27 Comparison of vascular reactivity in normal and hypertensive subjects.
- 1.2 Detection, Diagnosis and Treatment of Hypertension.
 - 1.2.1 Studies of alpha methyl dopa.
 - 1.2.2 Reserpine and related alkaloids in treatment.
 - 1.2.3 Hydralazine and other vasodilator drugs.
 - 1.2.4 Guanethidine and bethanidine as antihypertensive agents.
 - 1.2.5 Development of new antihypertensive drugs.
 - 1.2.6 How do diuretics lower blood pressure?
 - 1.2.7 Therapeutic agents affecting the sympathetic nervous system.

- 1.2.8 How do beta blocking drugs work to lower blood pressure?
- 1.2.9 Research on most effective drug combinations.
- 1.2.10 Research into once-a-day medication schedule for hypertensives.
- 1.2.11 To devise ways of reducing the cost of drugs.
- 1.2.12 The development of better administrative procedures to permit development and release of new antihypertensive, diuretic, and other cardiovascular drugs.
- 1.2.13 To develop more efficient ways for detecting secondary hypertension.
- 1.2.14 Development of better devices for recording blood pressure.
- 1.2.15 The hypertension problem as it exists in children and adolescents.
- 1.2.16 The relation of basal, causal, and continuous integrated blood pressure recording with the likelihood of future cardiovascular complications.
- 1.2.17 Research on most effective methods for screening and follow-up treatment.
- 1.2.18 Test feasibility and effectiveness of using "hypertensive" nurse to complement screening and treatment methods (particularly with local family physicians) currently in use.
- 1.2.19 Research on minimum work-up of hypertensive patients that will be effective.
- 1.2.20 To extend research on treating hypertension in patients with varying degrees of kidney disease.
- 1.2.21 What to do for high, unusual and borderline hypertension.
- 1.2.22 Clinical therapeutic trials in borderline hypertension.
- 1.2.23 Reversibility of hypertension exclusive of surgically curable forms.
- 1.2.24 Improvement of treatment of hypertensive emergencies.
- 1.2.25 To determine: Can effective antihypertensive treatment prevent or improve coronary insufficiency and prevent the occurrence of heart attack?
- 1.2.26 Demonstration unit throughout the country for detection, diagnosis and treatment of hypertension.
- 1.2.27 Demonstration units for improving patient compliance (quality of care).
- 1.2.28 The use of computers in diagnosis, prevention and treatment of hypertension.
- 1.2.29 Physicians' and nurses' education in use of antihypertensive drugs and diet.
- 1.2.30 Education and system development for paramedical and nurse helpers to treat and follow-up hypertensive patients.
- 1.2.31 Education of the public as to value of treating hypertension.
- 1.2.32 The training of manpower to accomplish the research objectives of the hypertension problem.
- 1.3 Cardiovascular Consequences of Hypertension.
 - 1.3.1a Hypertension and atherosclerosis.
 - 1.3.1b Hypertension and atherosclerosis (addendum).
 - 1.3.2 Hypertension and peripheral vascular disease.
 - 1.3.3 Hypertension and vascular disease.
 - 1.3.4 Cardiac hypertrophy and failure in hypertension.

DATA SUMMARY FOR
TASK GROUP 5

STROKE

PROBLEM 1. STROKE

1.1 Risk Factors Associated with Each Phase of Stroke Pathogenesis.

- 1.1.1 Risk factors before stroke: Environmental and genetic factors in hypertension.
- 1.1.2 Risk factors before stroke: Obesity.
- 1.1.3 Risk factors before stroke: Natural history of high blood pressure.
- 1.1.4 Risk factors before stroke: Hyperglycemia and abnormal insulin response.
- 1.1.5 Risk factors before stroke: Biological aging.
- 1.1.6 Risk factors before stroke: Thrombosis and embolization.
- 1.1.7 Risk factors before stroke: Cerebral aneurysms.
- 1.1.8 Risk factors during stroke: Autoregulation abnormalities.
- 1.1.9 Risk factors during stroke: Cerebral metabolic abnormalities.
- 1.1.10 Risk factors during stroke: Blood abnormalities.
- 1.1.11 Risk factors during stroke: Other risk factors.
- 1.1.12 Risk factors during stroke: Hypertension.
- 1.1.13 Risk factors during stroke: Metabolic abnormalities.
- 1.1.14 Risk factors during stroke: Cardiac and peripheral vascular disease.
- 1.1.15 Risk factors during stroke: Animal experimentation—factors in hemorrhages.
- 1.1.16 Risk factors after stroke: Recurrence and long-range factors.

1.2 Diagnostic Techniques Associated with Each Phase of Stroke Pathogenesis.

- 1.2.1 Diagnostic techniques before stroke: Intracranial and extracranial occlusive cerebral vascular disease.
- 1.2.2 Diagnostic techniques before stroke: Development of improved resolving systems for use in nuclear medicine procedures.
- 1.2.3 Diagnostic techniques before stroke: Isotopic assessment of heart and vessel walls in patients with transient ischemic attacks.
- 1.2.4 Diagnostic techniques before stroke: Prediction of outcome of transient ischemic attack by virtue of assessment of number and type of lesions in blood vessels as depicted by angiography.
- 1.2.5 Diagnostic techniques before stroke: Improved safety of catheterization guide lines.
- 1.2.6 Diagnostic techniques before stroke: Improvement of catheter materials for angiography.
- 1.2.7 Diagnostic techniques before stroke: Improvement of radiologic image intensifiers.
- 1.2.8 Diagnostic techniques before stroke: Improvement of X-ray tubes.
- 1.2.9 Diagnostic techniques before stroke: Improvement of film changers.
- 1.2.10 Diagnostic techniques before stroke: Improvement of the contrast material used for radiologic angiographic procedures.
- 1.2.11 Diagnostic techniques before stroke: Improvement of imaging systems.
- 1.2.12 Diagnostic techniques before stroke: Development of tomographic means for assessing angiograms.
- 1.2.13 Diagnostic techniques before stroke: Improvement of methods of assessment of blood flow with angiographic densimetric means.

- 1.2.14 Diagnostic techniques during stroke: Vascular disease.
 - 1.2.15 Diagnostic techniques during stroke: Intracranial and extracranial occlusive cerebral vascular disease.
 - 1.2.16 Diagnostic techniques during stroke: Monitoring cerebral blood flow and collateral circulation in acutely ill patients.
 - 1.2.17 Diagnostic techniques during stroke: Improvement of subtraction techniques in angiography.
 - 1.2.18 Diagnostic techniques during stroke: Development of methods for clot detection in vessels.
 - 1.2.19 Diagnostic techniques during stroke: Prediction of prognosis based on evaluation of size of stroke lesion by computerized axo-tomography.
 - 1.2.20 Diagnostic techniques during stroke: Assessment of factors involved in blood rheology, thrombogenesis and hemorrhage.
 - 1.2.21 Diagnostic techniques during stroke: Development and evaluation of methods for improved detection and diagnosis of intracranial hemorrhage.
 - 1.2.22 Diagnostic techniques during stroke: Evaluation of metabolic change in area of stroke by computerized axial tomogram (CAT).
 - 1.2.23 Diagnostic techniques during stroke: Development of model for isotopic assessment of CSF metabolism and flow before, during and after ischemic and hemorrhagic stroke.
 - 1.2.24 Diagnostic techniques during stroke: Continued study of metabolism of brain using radioactive isotopes.
 - 1.2.25 Diagnostic techniques during stroke: Detection and diagnosis of brain edema and intracranial hypertension.
 - 1.2.26 Diagnostic techniques after stroke: Methods for detection of newly developing vascular pathology and factors compromising recovery in stroke patients and for general assessment of their cardiovascular status.
- 1.3 Therapeutic Modalities Associated with Each Phase of Stroke Pathogenesis.
- 1.3.1 Therapy before stroke: Hypertension.
 - 1.3.2 Therapy before stroke: Obesity.
 - 1.3.3 Therapy before stroke: Thrombosis and embolization.
 - 1.3.4 Therapy before stroke: Transient ischemic attacks (TIA).
 - 1.3.5 Therapy before stroke: Surgical therapy for intra- and extracranial vascular disease.
 - 1.3.6 Therapy before stroke: Cardiovascular disease.
 - 1.3.7 Treatment before stroke: Community resources.
 - 1.3.8 Treatment during stroke: Acute hospital care—the stroke team.
 - 1.3.9 Treatment during stroke: Emergency room policies.
 - 1.3.10 Treatment during stroke: Evaluation of treatment in intensive care facilities.
 - 1.3.11 Treatment during stroke: Improvement of the patient handling systems in radiology.
 - 1.3.12 Treatment during stroke: Rehabilitation techniques during the acute stroke stages.
 - 1.3.13 Treatment during stroke: Subarachnoid hemorrhage—aneurysm.
 - 1.3.14 Treatment during stroke: Hypertensive intracerebral hemorrhage.
 - 1.3.15 Treatment during stroke: Spasm.

- 1.3.16 Treatment during stroke: Mechanism of CO₂ responsiveness and abnormalities present in stroke.
- 1.3.17 Treatment during stroke: Role of regional metabolism in regulation of regional cerebral blood flow and derangements that occur in stroke.
- 1.3.18 Treatment during stroke: Development of better methods for assessing cerebral blood flow by angiographic techniques to be used in patients with blood vessel spasm.
- 1.3.19 Treatment during stroke: Role of neural innervation of cerebral vessels in regulation of cerebral blood flow and abnormalities in stroke.
- 1.3.20 Treatment during stroke: Physiologic and metabolic methodology.
- 1.3.21 Treatment after stroke: Restoration of motor function—control of spasticity.
- 1.3.22 Treatment after stroke: Restoration of motor function—motor control.
- 1.3.23 Treatment after stroke: Communication disorders of stroke patients.
- 1.3.24 Treatment after stroke: Restoration of sensory loss.
- 1.3.25 Treatment after stroke: Utilization of behavior modification in stroke rehabilitation.
- 1.3.26 Treatment after stroke: The quantitative determination of the effectiveness of rehabilitation for patients with a completed stroke.
- 1.3.27 Treatment after stroke: Determination of prediction of recovery of levels of function following a stroke.
- 1.3.28 Prevention, detection, diagnosis, treatment and management of stroke in children.

DATA SUMMARY FOR
TASK GROUP 6

CONGENITAL HEART DISEASE



PROBLEM 1. CONGENITAL HEART DISEASE

- 1.1 Viral Agents.
 - 1.1.1 Serological studies—serum banks: (a) maternal seroconversions, (b) high newborn IgM—specific IgM.
 - 1.1.2 Virus isolation: (a) direct culture, (b) fluorescence of tissues.
 - 1.1.3 Epidemic correlations: (a) document maternal infections, (b) determine fetal effects.
 - 1.1.4 Experimental animals using "human" viruses: (a) primates, (b) smaller animals.
- 1.2 Exploration of Genetic Factors in the Etiology of Congenital Heart Diseases.
 - 1.2.1 Single mutant gene etiology: syndrome identification and investigation in depth of specific syndromes having cardiovascular maldevelopment as a feature.
 - 1.2.2 Single mutant gene etiology: biochemical identification.
 - 1.2.3 Reevaluation of possible chromosomal etiology of "nonsyndrome," congenital heart disease by the new banding techniques with potential utilization of computer karyotype analysis.
 - 1.2.4 Multifactorial inheritance: genetic predisposition—human studies.
 - 1.2.5 Multifactorial inheritance: genetic predisposition—animal studies.
 - 1.2.6 Multifactorial inheritance: environmental triggers—human studies.
 - 1.2.7 Environmental triggers: animal studies.
- 1.3 Teratogenic Agents in Congenital Heart Disease.
 - 1.3.1 Embryogenesis, pathogenesis and teratogenic agents.
 - 1.3.2 Hemodynamic factors in cardiac maldevelopment.
 - 1.3.3 Animal models for drug testing.
 - 1.3.4 Close scrutiny of drugs with possible teratogenic potential in man.
 - 1.3.5 Training needs in regard to the above projects.
- 1.4 Identification of Causative Agents, or Risk Factors, of Congenital Heart Disease.
 - 1.4.1 Investigation of natural clusters of congenital heart disease.
 - 1.4.2 Prospective identification of pregnancy outcome in high-risk populations; offspring of parents with congenital heart disease.
 - 1.4.3 Identification of pregnancy outcome in high-risk populations; offspring of mothers in whom maternal viral infection occurred during pregnancy.
 - 1.4.4 Prospective identification of pregnancy outcome in high-risk populations; offspring of parents exposed to potential teratogens or known carcinogens.
 - 1.4.5 Establishment of an embryo bank.
 - 1.4.6 Validation through preplanned clinical observation of suspected etiologic correlates.
- 1.5 The Recognition of Infants with Critical Congenital Heart Disease.
 - 1.5.1 Improved interhospital emergency transportation.
 - 1.5.2 Improvement of interhospital communications.
 - 1.5.3 Professional education of newborn nursery personnel.
 - 1.5.4 Development of instrumentation to count respiration and measure arterial oxygen saturation indirectly in newborn infants.

- 1.6 Noninvasive Diagnostic Techniques.
 - 1.6.1 Echocardiography and other techniques.
- 1.7 Normal Fetal and Neonatal Cardiovascular Functions, and Mechanisms of Cardiocirculatory Adaptations to Perinatal Disorders, Congenital and Acquired.
 - 1.7.1 Characterization of the intrinsic properties of the normal cardiovascular system during embryogenesis, fetal and postnatal development.
 - 1.7.2 Characterize the influence upon normal cardiocirculatory development of maternal factors and concurrent development of the respiratory, renal and central and autonomic nervous systems.
 - 1.7.3 Time-related, embryologic, fetal and postnatal adaptation to natural and pathological environmental abnormalities.
 - 1.7.4 Time-related embryologic, fetal and postnatal adaptation to fetal and neonatal disorders.
 - 1.7.5 Mechanisms of ductal closure.
- 1.8 Diagnosis and Possible Treatment of Congenital Heart Disease in Fetuses before Birth.
 - 1.8.1 Diagnosis of congenital heart disease by amniocentesis.
 - 1.8.2 Diagnosis of congenital heart disease in utero.
 - 1.8.3 Development of techniques for correction of congenital heart defects in utero.
- 1.9 Predictability and Prevention of Pulmonary Vascular Disease in Congenital Heart Disease.
 - 1.9.1 Identification, evaluation and treatment of infant patients at risk for pulmonary vascular obstruction.
 - 1.9.2 Research into pathogenesis.
- 1.10 Surgical Treatment.
 - 1.10.1 Surgery in the neonate and small infants: (a) techniques; (b) anesthesia; and (c) monitoring.
 - 1.10.2 Percutaneous palliation and treatment.
 - 1.10.3 Evaluation of "corrective" operations.
- 1.11 Habilitation and Rehabilitation of the Patient with Operated and Unoperated Congenital Heart Defects.
 - 1.11.1 Development of noninvasive techniques to follow severity of congenital heart disease.
 - 1.11.2 Work capacity evaluation.
 - 1.11.3 Recreational activity.
 - 1.11.4 Vocations.
 - 1.11.5 Life insurance.
 - 1.11.6 Support regarding emotional impact on patient and family.
 - 1.11.7 Cardiopulmonary support techniques.
 - 1.11.8 Unnatural history after surgical intervention.

DATA SUMMARY FOR
TASK GROUP 7

RHEUMATIC AND OTHER VALVULAR HEART DISEASES



PROBLEM 1. RHEUMATIC AND OTHER VALVULAR HEART DISEASES

- 1.1 Control and Early Treatment of Beta-Streptococcal Infection to Prevent Initial and Recurrent Attacks of Rheumatic Fever.
 - 1.1.1 Education: (a) professional, (b) nonprofessional, (c) motivational studies.
 - 1.1.2 Development of new techniques for identification of beta-streptococcal infections.
 - 1.1.3 More extensive implementation of currently available techniques for the identification of beta-streptococcal infections.
 - 1.1.4 Prevalence and incidence surveillance of beta-streptococcal infection.
 - 1.1.5 Epidemiologic surveys of acute rheumatic fever and chronic rheumatic heart diseases, including support of multiphasic screening tests.
 - 1.1.6 Development and evaluation of new antibiotics effective against beta-streptococci.
- 1.2 Prevention of Streptococcal Infections in Rheumatic Subjects.
 - 1.2.1 Compliance evaluation methods.
 - 1.2.2 Duration of prophylaxis necessary to prevent secondary attacks of rheumatic fever.
 - 1.2.3 Reasons for prophylaxis failure.
 - 1.2.4 Evaluation of prophylaxis regimens.

Professional education (Medical students, practicing physicians, health care personnel) is covered in Project Area 1.1.1.

Layman education (Patients and parents, health education) is covered in Project Area 1.1.1.

Development of alternative antibiotics is covered in Project Area 1.1.6.

Development of a streptococcal vaccine is covered in Project Area 1.3.7.
- 1.3 Determine the Biologic Properties of Group A Streptococci
 - 1.3.1 Bacterial physiology and morphology.
 - 1.3.2 Identification and characterization of cellular and extracellular antigens and toxins.
 - 1.3.3a Streptococcal antigens cross-reactive with mammalian tissue.
 - 1.3.3b The role of Group A streptococci in the pathogenesis of rheumatic fever.
 - 1.3.4 Methods for serologic identification of streptococci.
 - 1.3.5a Immunological and pathological responses to streptococcal antigens and products.
 - 1.3.5b Immunological and pathological responses to streptococcal antigens and products (addendum).
 - 1.3.6 Experimental models of streptococcal and L-form infection and response.
 - 1.3.7 Vaccine development.
 - 1.3.8 New approaches to immunization.
- 1.4 Quantitative Assessment of Cardiopulmonary Function by Exercise Testing.
 - 1.4.1 Development of an integrated system for exercise testing.
 - 1.4.2 Development of a noninvasive respiratory gas method for blood flow measures during exercise.
 - 1.4.3 Quantitative assessment of cardiopulmonary function with standardized exercise testing.

- 1.5 Reduce the Effects of Rheumatic Heart Disease.
 - 1.5.1 Methods for detection of rheumatic heart disease.
 - 1.5.2 Improved methods for assessment of valvular and myocardial function.
 - 1.5.3 Improved techniques for prevention and treatment of bacterial endocarditis.
 - 1.5.4 Improved surgical management of chronic valve disease.
 - 1.5.5 Physical and psychological rehabilitation of rheumatic heart disease patient's long-term follow-up—smooth transition to adulthood.
 - 1.5.6 Nonrheumatic valvular disease.
- 1.6 Reduce the Effects of Acute Rheumatic Fever.
 - 1.6.1 Improved diagnostic techniques.
 - 1.6.2 Necessary improved diagnostic techniques—test of rheumatic fever activity.
 - 1.6.3 Improved therapy and better methods to evaluate therapy activity.
 - 1.6.4 Cooperative study of natural history of rheumatic fever.
 - 1.6.5 Education of physicians and students about rheumatic fever.
 - 1.6.6 Physical and emotional rehabilitation studies of rheumatic fever.
 - 1.6.7 Chronic or prolonged rheumatic fever.
- 1.7 Identification of Risk Factors in Rheumatic Fever.
 - 1.7.1 Evaluation of the role in pathogenesis of the biologic properties of the infecting streptococcal strain.
 - 1.7.2 Evaluation of the contribution to rheumatic fever incidence and morbidity of poor housing, crowding, sanitary conditions and malnutrition.
- 1.8 Immunologic and Immunopathologic Studies in Rheumatic Fever Patients.
 - 1.8.1 Immunopathologic and histopathologic study of biopsy and post mortem tissues of patients with rheumatic fever.
 - 1.8.2 Nature and quantitation of humoral and cellular immune responses to streptococcal infection in rheumatic fever.
 - 1.8.3 The role of autoimmunity as indicated by the humoral and cellular immune responses related to streptococcal cross-reactive antigens and autoantigens.
 - 1.8.4 The response of rheumatic fever to chemotherapeutic and immunosuppressive agents.
- 1.9 Modification of Illness Behavior.
 - 1.9.1 Psychosocial and cultural aspects to susceptibility to beta-streptococcal infection and rheumatic fever.
 - 1.9.2 Evaluation of educational techniques directed towards children and adults re: beta-streptococcal infection and RF/RHD.
 - 1.9.3 Studies of medical staff-patient-parent communication.
 - 1.9.4 Studies of motivation to seek medical attention for beta-streptococcal infection in high-risk groups.
 - 1.9.5 Studies of psychological responses and adaptation to chronic illness (i.e., RF and RHD).
- 1.10 The Detection, Treatment, Rehabilitation and Education of Adult Patients with Acute Rheumatic Fever and/or Rheumatic Heart Disease.
 - 1.10.1 Recognition and diagnosis of acute rheumatic fever and rheumatic heart disease in adult patients.

- 1.10.2 Education of the public and medical professions in regard to the prevention of acute rheumatic fever in adults, the symptoms and treatment of acute rheumatic fever and of chronic rheumatic heart disease in adult patients.
 - 1.10.3 Education of the public and physicians and patients with known rheumatic heart disease regarding the appropriate follow-up of patients with rheumatic heart disease including antibiotic prophylaxis.
 - 1.10.4 Study of special problems in adult females with rheumatic heart disease: (a) selection in use and safety of contraceptives (b) medical and obstetrical management during pregnancy, (c) problems associated with anticoagulation for either pulmonary emboli, arterial emboli, or prosthetic valves.
 - 1.10.5 Provision of adequate follow-up for medical and surgical management of patients with rheumatic heart disease and determination of the natural history of rheumatic fever, rheumatic heart disease with medical therapy and the results of surgical therapy of various types of patients with rheumatic heart disease.
- 1.11 Evaluation of the Role of Viral Infection in Endomyocarditis and Chronic Valvular Disease.
- 1.11.1 Role of Coxsackie viral infection and other viruses in chronic valvular disease in man and in experimental animals. Epidemiologic and serologic surveys of viral infection in patients with endocarditis and valvular disease.

DATA SUMMARY FOR
TASK GROUP 8

CARDIOMYOPATHY



PROBLEM 1. CARDIOMYOPATHY

- 1.1 Study of Factors which May Affect Susceptibility to Myocardial Disease.
 - 1.1.1 Development of an animal model for testing susceptibility factors in myocardial disease.
 - 1.1.2 How is increased susceptibility to myocardial disease mediated?
- 1.2 Evaluation of Genetic Factors in Heart Muscle Disease.
 - 1.2.1 Identification, registry, and screening of subjects and their relatives with idiopathic heart muscle and familial neuromuscular disease.
- 1.3 Detection and Study of Nonviral Infectious Myocarditis.
 - 1.3.1 Clinico-pathologic studies of nonviral infectious myocarditis.
 - 1.3.2 Development and study of experimental models of nonviral, infectious myocarditis.
 - 1.3.3 Basic scientific studies of myocardial effects of bacteria, Rickettsia, fungi, and protozoa.
- 1.4 Significance of Nutritional Factors in Cardiomyopathy.
 - 1.4.1 Studies of nutritional deficiencies in experimental animals, including effects of maternal nutritional deficiencies upon offspring.
 - 1.4.2 Obesity heart disease—studies of prevalence and reversibility in obese subjects.
 - 1.4.3 Identification of populations and individuals with a high prevalence of nutritional deficiencies and screening them for evidence of myocardial disease.
 - 1.4.4 Screening of populations with a high incidence of myocardial disease for evidence of nutritional deficiency.
- 1.5 Evaluation of Immune Factors in Heart Muscle Disease.
 - 1.5.1 Study of patients with heart muscle disease of unknown cause (including endomyocardial fibrosis) for evidence of immune mechanisms (including serologic studies, skeletal muscle studies for evidence of bound antimyocardial globulin and complement in cardiac muscle biopsy).
 - 1.5.2 Development of an animal model of autoimmune heart disease.
 - 1.5.3 Study of patients with ischemic, infectious (Chagas, viral myocarditis) or traumatic injury to the myocardium for evidence of immune factors and correlation with their clinical course.
 - 1.5.4 Development of new tests and increased availability of tests for evaluation of immune mechanisms in myocardial disease, e.g., cellular plus humoral-common antigen or antigen to altered myocardium.
 - 1.5.5 Studies of animal models of heart disease for immune mechanisms (posttrauma, post-radiation, postisoproterenol, use of experimental antiheart antibodies, Coxsackie B myocarditis in mice).
- 1.6 Cardiomyopathy Due to Physical Agents.
 - 1.6.1 Risk factors in cardiomyopathy due to physical agents.
 - 1.6.2 Immune mechanisms in cardiomyopathy due to physical agents.
 - 1.6.3 Effects of immunosuppressive agents upon cardiomyopathy in rabbits.
 - 1.6.4 Study of patients undergoing irradiation therapy for evidence of susceptibility (risk) factors for cardiomyopathy.

- 1.7 To Establish the Role of Various Pharmacologic and Toxic Agents in the Production of Cardiomyopathy.
 - 1.7.1 Anatomic study of changes in the cardiovascular system in experimental animals exposed to various therapeutic and potentially toxic agents.
 - 1.7.2 Acute and chronic study of cardiovascular function changes occurring in experimental animals exposed to various therapeutic and potentially toxic agents.
 - 1.7.3 Anatomic study of changes in the cardiovascular system in man exposed to various therapeutic and potentially toxic agents.
 - 1.7.4 Acute and chronic study of cardiovascular function changes occurring in man exposed to various therapeutic and potentially toxic agents.
 - 1.7.5 Biochemical approach to mechanism of production of structural and functional abnormalities in cardiomyopathies of toxic origin.
 - 1.7.6 The definition of safe dosages and exposure levels for potentially cardiotoxic agents.
 - 1.7.7 Professional and public education relative to safe dosages and exposure levels for potentially cardiotoxic agents.
 - 1.7.8 Comparative studies of anatomic and physiologic changes induced by various drugs given in equally therapeutic doses.
 - 1.7.9 A study of toxicity-blocking but therapeutic-preserving agents for use in combination with drugs having potential cardiotoxic propensities.
- 1.8 Determination of the Role of Alcohol in Cardiomyopathy.
 - 1.8.1 Modification by exogenous factors.
 - 1.8.2 Define quantitative and temporal aspects.
 - 1.8.3 Establish incidence and type of cardiomyopathy in the alcoholic population.
 - 1.8.4 Animal models to define morphologic, biochemical and functional abnormalities.
 - 1.8.5 Incidence of sudden death in young alcoholics.
 - 1.8.6 Acute cardiac effects of ethanol.
- 1.9 To Establish the Importance of Conduction System Abnormalities and Rhythm Disturbances in the Clinical Expression and Natural History of the Cardiomyopathies.
 - 1.9.1 A study of the incidence and type of conduction system abnormalities and rhythm disturbances occurring in systematic cardiomyopathic patients monitored continuously.
 - 1.9.2 Electrophysiologic studies in experimentally induced cardiomyopathy.
 - 1.9.3 Anatomic study of conducting system in experimentally induced cardiomyopathy.
 - 1.9.4 A study of disability in cardiomyopathy directly attributable to conduction system abnormalities and rhythm disturbances.
 - 1.9.5 A study of mechanisms of sudden death occurring in patients with cardiomyopathy.
 - 1.9.6 A study of prevalence and type of cardiomyopathy occurring in patients with sudden death.
 - 1.9.7 The prophylactic use of antiarrhythmic agents in management of patients with cardiomyopathy.
 - 1.9.8 Use of antiarrhythmic agents lacking negative inotropic effects in management of patients with cardiomyopathy.

1 9 9 The place of artificial cardiac pacing in management of patients with cardiomyopathy.

1.10 Skeletal and Heart Muscle Studies in Patients.

1.10.1 Utility of peripheral blood for diagnosis.

1.10.2 Tissue sampling methods.

1.10.3 Biochemical studies: Energy production.

1.10.4 Biochemical studies: Excitation.

1.10.5 Biochemical studies: E-C coupling.

1.10.6 Biochemical studies: Control systems.

1.10.7 Biochemical studies: Contraction.

1.10.8 Physiological studies: Excitation.

1.10.9 Physiological studies: Contraction.

1.10.10 The processes of hypertrophy.

1.10.11 Morphological studies.

1.10.12 Pharmacological studies.

1.10.13 Diagnostic precision: Distinction from ischemic heart disease.

1.10.14 Studies of normal myocardium.

1.11 Myocardial Effects of Altered Endocrine Function.

1.11.1 To define the relative significance of blood vessel and myocardial pathology in diabetes mellitus.

1.11.2 Definition of the cardiac status in hyper- and hypothyroidism.

1.11.3 Studies of the pathogenesis of cardiac injury due to catecholamine excess.

1.11.4 To define the role of hyperparathyroidism in myocardial abnormalities of uremia.

1.12 To Identify Mechanisms and the Importance of Thromboembolic Disorders in the Clinical Expression and Natural History of the Cardiomyopathies and Improve Means of Prevention, Detection and Treatment.

1.12.1 A study of hemotologic factors and cardiac tissue factors in the development of mural thrombi in experimentally induced cardiomyopathy.

1.12.2 A clinical and laboratory study of the incidence of thromboembolic phenomena in various cardiomyopathies.

1.12.3 A study of the use of radioactive fibrinogen in the detection and quantitation of mural thrombogenesis in experimentally induced cardiomyopathy.

1.12.4 A study of the use of radioactive fibrinogen in the detection and quantitation of mural thrombogenesis in humans with cardiomyopathy.

1.12.5 Use of radioangiographic techniques in the detection and quantitation of mural thrombogenesis in experimentally produced cardiomyopathy.

1.12.6 Use of radioangiographic techniques in the detection and quantitation of mural thrombogenesis in cardiomyopathy of man.

1.12.7 A controlled study on the use of various antithrombotic agents in the prevention and treatment of thromboembolism occurring in experimentally induced cardiomyopathy.

- 1.12.8 A controlled study on the use of various antithrombotic agents in the prevention and treatment of thromboembolic phenomena occurring in man with cardiomyopathy.
- 1.13 Pericardial Disease and Cardiomyopathy.
 - 1.13.1 Pericarditis as a presentation of cardiomyopathy.
 - 1.13.2 Myocardial involvement in primary pericardial disease.
- 1.14 Obstructive Cardiomyopathy (IHSS).
 - 1.14.1 Pathogenesis.
 - 1.14.2 Natural history.
 - 1.14.3 Evaluation of therapy.
 - 1.14.4 Hemodynamic determinants.
- 1.15 Development and Utilization of Artificial and Naturally Occurring Animal Models of Human Cardiomyopathy.
 - 1.15.1 Identification of naturally occurring animal cardiomyopathy.
 - 1.15.2 Development of animal models of cardiomyopathy of known exogenous etiology.
- 1.16 Senile Cardiomyopathy.
 - 1.16.1 To describe the cardiac function in clinically healthy humans from the fifth to tenth decades of life.
 - 1.16.2 To evaluate the coronary arteries in the aged myocardium.
 - 1.16.3 To define in animal models the changes in composition of the myocardial interstitium and in the cardiac cell related to aging.
- 1.17 Viral Diagnostic Methods.
 - 1.17.1 Increased availability of methods of isolation and identification of viruses and sero diagnosis, including establishment of viral diagnostic centers.
 - 1.17.2 Development of new immunofluorescent techniques for rapid identification of viruses.
 - 1.17.3 Education of health care providers to symptoms and signs of myocarditis and availability of diagnostic techniques.
 - 1.17.4 Studies of incidence and nature of cardiac involvement in specific viral infection, taking advantage of sporadic outbreaks or epidemics.
 - 1.17.5 Inter-institutional (regional) studies of clinical manifestations and causes of acute myocarditis and sequelae.
 - 1.17.6 Controlled trials of therapy.
 - 1.17.7 Study of mechanism of virus action upon the heart.
- 1.18 Early Detection of Myocardial Dysfunction.
 - 1.18.1 Assessment of usual catheterization data in detecting myocardial dysfunction.
 - 1.18.2 Assessment of cardiac chamber volume parameters, force-velocity parameters, and other newer techniques for studying myocardial function.

- 1.18.3 Study of relationships between invasive (from cardiac catheterization) and non-invasive techniques for detecting myocardial dysfunction.
- 1.18.4 Study of various means of stress in detecting subtle myocardial dysfunction.
- 1.18.5 Development of cardiac muscle biopsy instrumentation.
- 1.19 To Detect Cardiomyopathy Early in Course and Attempt to Reverse Mild Abnormalities.
 - 1.19.1 Use of noninvasive techniques to evaluate ventricular function in children and adults at risk for early detection.
 - 1.19.2 To establish animal models for interval (repeated) examination of morphologic, functional and biochemical abnormalities.
 - 1.19.3 To determine environmental factors which retard or accelerate progression.
- 1.20 Treatment of Congestive Heart Failure in Cardiomyopathy.
 - 1.20.1 Comparison of response to therapy of congestive heart failure in cardiomyopathy versus heart failure of other etiology.
 - 1.20.2 Controlled evaluation of specific drugs and interventions in the treatment of congestive heart failure in cardiomyopathy.
 - 1.20.3 The role of antiinflammatory agents in the treatment of congestive heart failure in acute myocarditis.
 - 1.20.4 Controlled study of possible effects of agents supporting protein synthesis in the therapy of the failing cardiomyopathic heart.
 - 1.20.5 Use of existing and development of new animal models of myopathic congestive heart failure for the study of different therapeutic approaches.
- 1.21 Improvement of Therapy.
 - 1.21.1 Antiarrhythmic therapy without negative inotropism.
 - 1.21.2 Positive inotropy without arrhythmogenesis.
 - 1.21.3 Studies of normal myocardium.
- 1.22 Physical Activity in Cardiomyopathy.
 - 1.22.1 Study of the effects of acute exercise stress upon cardiac function in cardiomyopathy.
 - 1.22.2 Study of physical exercise programs for possible conditioning effects upon the heart and in relation to cardiomyopathy.
 - 1.22.3 Study of the effects upon the myocardium and correlation of rest or limitation of activity in patients with cardiomyopathy.
- 1.23 Characterization of Primary Heart Muscle Disease With and Without Associated Neuromuscular Disorders.
 - 1.23.1 Identification and registry of patients with primary cardiac muscle disease and their families.
 - 1.23.2 Delineation of specific disease entities within primary cardiac muscle disease.
 - 1.23.3 Definition of basic defects in specific forms of primary cardiac muscle disease.
 - 1.23.4 Studies of normal human myocardium.
- 1.24 Cardiomyopathy Registries.
 - 1.24.1 Establishment of cardiomyopathic registries.
 - 1.24.2 Development of standard format for collection of data from patients with cardiomyopathy.

- 1.24.3 Development of classification and staging of cardiomyopathy.
- 1.24.4 Development of educational materials on cardiomyopathy for health care personnel and patients.
- 1.24.5 Establishment of laboratories to test myocardial toxicity of drugs, food additives, industrial chemicals, and other environmental hazards in experimental animals and in man.
- 1.25 To Establish the Importance of the Peripartal State in the Production of Cardiomyopathy and Improve Methods of Prevention, Early Detection, Management and Rehabilitation.
 - 1.25.1 An attempt to produce cardiomyopathy in the experimental animal with biological material derived from patients with PPCM.
 - 1.25.2 An experimental study of the influence of peripartal state on the effects of potentially cardiotoxic agents and cardiotropic infectious agents.
 - 1.25.3 Viral isolation and serologic study of peripartal patients compared with age-sex matched nonpregnant patients.
 - 1.25.4 Potential effects of diuretics development of PPCM.
 - 1.25.5 Detailed peripartal monitoring of high risk for development of cardiomyopathy (over 30 years old, third pregnancy, toxemia, twins, poverty areas).
 - 1.25.6 Controlled study of use of long-term bedrest in management of patients with PPCM.
 - 1.25.7 Controlled study of use of standard anticoagulant and other antithrombotic agents in management of patients with PPCM.
 - 1.25.8 Study of use of supplemental therapy of CHF with preparations related to protein synthesis.
 - 1.25.9 Study of oral contraceptives without thrombogenic properties.
- 1.26 Myocarditis and Cardiomyopathy in Infants and Children.
 - 1.26.1 Antenatal and neonatal myocarditis and relationship of immune mechanisms in the neonate to development of myocarditis due to virus or other agents.
 - 1.26.2 Hypertrophic cardiomyopathy in infants and children.
 - 1.26.3 Etiology and pathogenesis of endocardial fibroelastosis (EFE).
 - 1.26.4 Follow-up of acute myocarditis in childhood as a possible cause for chronic cardiomyopathy.
 - 1.26.5 Cardiomyopathy related to glycogen storage disease (GSD).

DATA SUMMARY FOR
TASK GROUP 9

ARRHYTHMIAS



PROBLEM 1. VENTRICULAR ARRHYTHMIAS AND FIBRILLATION

- 1.1 Determination of Susceptibility of Populations and Individuals to Ventricular Arrhythmias and Fibrillation.
 - 1.1.1 Identification of susceptible populations.
 - 1.1.2 Identification of predisposed individuals.
 - 1.1.3 Determination of circumstances of occurrence (i.e., stress, pacing, exercise).
- 1.2 Prophylaxis of Arrhythmias in High-Risk Groups.
 - 1.2.1 Development of suitable drugs for long-term prophylaxis.
 - 1.2.2 Development of animal models for testing treatment modalities.
 - 1.2.3 Clinical testing of susceptible populations with existing or newly developed drugs.
 - 1.2.4 Development of instrumentation for detection and quantification of arrhythmias.
 - 1.2.5 Development of techniques for analysis and reduction of instrumentation readings and other data.
 - 1.2.6 Development of cellular or subcellular models for pharmacologic testing.
 - 1.2.7 Determination of structure/activity relationship of antirhythmic drugs.
 - 1.2.8 Early prehospital use of drugs for the prevention of sudden death.
- 1.3 Identification of Factors Contributing to Individual Susceptibility to Ventricular Arrhythmias and Fibrillation.
 - 1.3.1 Determination of the role of the nervous system (autonomic and central) in ventricular arrhythmia and fibrillation.
 - 1.3.2 Determination of the causative role of pharmacological agents in ventricular arrhythmia and fibrillation.
 - 1.3.3 Determination of familial influences in the occurrence of ventricular arrhythmias and fibrillation.
 - 1.3.4 Determination of the role of noncardiovascular conditions as contributing factors to ventricular arrhythmias and fibrillation.
 - 1.3.5 Determination of the role of primary myocardial disease in ventricular arrhythmias and fibrillation.
 - 1.3.6 Determination of the role of coronary circulation in ventricular arrhythmias and fibrillation.
 - 1.3.7 Determination of the role of valvular diseases in ventricular arrhythmias and fibrillation.
 - 1.3.8 Animal models for the study of factors contributing to ventricular arrhythmias and fibrillation.
 - 1.3.9 Ischemia versus anoxia in ventricular arrhythmias and fibrillation.
 - 1.3.10 Determination of mechanism of fibrillation at cellular, suborgan, and organ levels.
 - 1.3.11 Determination of normal and aberrant molecular mechanisms for maintaining the cardiac cellular membrane potential.
 - 1.3.12 Pathological studies to identify risk factors.
 - 1.3.13 Determination of normal electrophysiologic mechanisms of impulse generation and propagation.
 - 1.3.14 Quantitative structural studies of conductive system.
 - 1.3.15 Studies of coronary circulation with respect to excitation and conduction (including

- small vessels).
- 1.3.16 Determination of the role and mechanism of innervation in ventricular arrhythmias and fibrillation.
- 1.3.17 Determine the role and validity of ECG as a prediction of ventricular fibrillation.
- 1.3.18 Development of increased resolution of ECG (i.e., high frequency, fine structure, etc.).
- 1.3.19 Determination of the molecular mechanisms of membrane functions.
- 1.3.20 Regulation and modulation of the conduction system (including adrenergic and cholinergic mechanisms and receptors).
- 1.3.21 Determination of mechanism of fibrillation at cellular and molecular levels.
- 1.4 Development of Instrumentation and Techniques for Early Detection of Ventricular Arrhythmias and Fibrillation.
 - 1.4.1 Development of externally or internally placed recording and monitoring devices.
 - 1.4.2 Development of distant data transmission and alarm systems.
- 1.5 Development and Application of Treatment Modalities.
 - 1.5.1 Development of better electrical devices for treatment of ventricular arrhythmias and fibrillation.
 - 1.5.2 Development of drugs for treatment of ventricular arrhythmias and fibrillation.
 - 1.5.3 Treatment of digitalis intoxication.
 - 1.5.4 Development of improved care delivery systems (including patient education, professional and paraprofessional education, and the logistics of care delivery).

PROBLEM 2. ASYSTOLE

- 2.1 Determine Mechanism of Asystole.
 - 2.1.1 Studies of the mechanism of electromechanical dissociation as viewed from an understanding of excitation-contraction coupling.
 - 2.1.2 Determination of the mechanisms of impulse formation and of failure of impulse.
 - 2.1.3 Studies of structural problems in impulse initiation and propagation.
 - 2.1.4 Determination of the mechanism of impulse propagation.
 - 2.1.5 ECG predictors or correlates of asystole.
 - 2.1.6 Studies of heart block associated with congenital causes: surgery, spontaneous acquired heart block; pathology.
 - 2.1.7 Identification of populations susceptible to asystole.
- 2.2 Development of Instrumentation and Techniques for Early Detection and Diagnosis of Asystole.
 - 2.2.1 Development of externally or internally placed recording and monitoring devices.
 - 2.2.2 Development of distant data transmission and alarm systems.
- 2.3 Early Restoration of an Effective Cardiac Rhythm.
 - 2.3.1 Development of drugs to promote initiation or conduction of impulse.
 - 2.3.2 Improvement of electrical pacing devices:
 - long-lived (energy source)
 - small size (pediatrics)
 - 2.3.3 Studies of atrio-ventricular bridge.

PROBLEM 3. ATRIAL ARRHYTHMIAS

- 3.1 Determination of Mechanism for Initiation and Sustaining Atrial Fibrillation and Other Atrial Arrhythmias.
 - 3.1.1 Determination of mechanism of atrial fibrillation.
 - 3.1.2 Determination of mechanisms of other atrial arrhythmias including Bradycardia tachycardia syndrome and mechanism of Wolff-Parkinson-White syndrome.
 - 3.1.3 Development of improved electrical diagnostic mapping.
- 3.2 Development of Therapeutic Techniques to Maintain Normal Sinus Rhythm.
 - 3.2.1 Development and testing of better drugs or drug combinations for treatment of atrial arrhythmias.
 - 3.2.2 Development of pacing techniques.
 - 3.2.3 Development of surgical approaches to WPW syndrome.
 - 3.2.4 Studies of electrical termination.

PROBLEM 4. CRIB DEATH

- 4.1 Determine the Etiology of, and Preventative Measures for, Crib Death.
 - 4.1.1 (1) Determination of the significance of eligibility factors identified by epidemiological studies of crib death. (2) Determination of the pathophysiological mechanisms involved in crib death.
 - 4.1.2 Determination of the role of AV and IV conduction in crib death.
 - 4.1.3 Determination of the role of autonomic control of the heart in crib death.
 - 4.1.4 Studies of electrolyte transport and metabolism in crib death.
 - 4.1.5 To reduce incidence of or eliminate crib death.

DATA SUMMARY FOR
TASK GROUP 10

CARDIAC FAILURE



PROBLEM 1. DIAGNOSIS/EVALUATION

- 1.1 Develop Methods for Diagnosis and Detection.
 - 1.1.1 Early detection of impending pulmonary edema.
 - 1.1.2 Methods of evaluating cardiac function requiring intravascular catheterization.
 - 1.1.3 Noninvasive evaluation of cardiac function.

PROBLEM 2. PATHOPHYSIOLOGY

- 2.1 Function of the Heart as an Organ in Cardiac Failure.
 - 2.1.1 Effect of pressure and volume load presented to normal and diseased heart (compliance, geometry, valve dysfunction).
 - 2.1.2 Development of animal models.
 - 2.1.3 Regulation of coronary circulation in cardiac failure (normal and diseased heart; includes pressure-volume changes, altered distribution and innervation).
 - 2.1.4 Lymphatic circulation.
 - 2.1.5 Regional dissociation of ventricular function.
 - 2.1.6 Impact of disordered rhythm on conduction in heart function.
 - 2.1.7 Role of abnormalities of cardiac skeleton in pathogenesis.
- 2.2 Mechanism of Disordered Contraction in Cardiac Failure.
 - 2.2.1 Energy production.
 - 2.2.2 Excitation-biochemistry.
 - 2.2.3 Excitation-contraction coupling-biochemistry.
 - 2.2.4 Contraction-biochemistry.
 - 2.2.5 Excitation-physiology.
 - 2.2.6 Contraction-physiology.
 - 2.2.7 Control mechanisms.
 - 2.2.8 Normal mechanisms.
- 2.3 Neurohumoral Control of Cardiac Function.
 - 2.3.1 Neural control of contraction and relaxation.
 - 2.3.2 Neural control of excitable properties.
 - 2.3.3 Neural control of metabolism.
 - 2.3.4 Humoral control of cardiac function.
 - 2.3.5 Nervous system integrative control of cardiac function.
 - 2.3.6 Cardiac afferent input to central nervous system.
 - 2.3.7 Disorders of adrenergic and cholinergic mechanisms in cardiac failure.
 - 2.3.8 Reinnervation of the extrinsically denervated heart.
- 2.4 Growth, Hypertrophy and Dedifferentiation.
 - 2.4.1 Initiation of growth.
 - 2.4.2 Mechanism of cardiac growth.

- 2.4.3 New vessel growth.
- 2.4.4 Connective tissue growth.
- 2.4.5 Myocardial cell growth and organization.
- 2.4.6 Altered structural and functional components.
- 2.4.7 Turnover and destruction of cell components; regression of cardiac hypertrophy.
- 2.4.8 Proliferation capacity of the heart muscle cell: Regeneration.
- 2.4.9 Functional capacity of hyperplastic versus hypertrophied heart: Cardiac failure: Congenital versus acquired cardiac disease.
- 2.5 Body Fluid Volume in Cardiac Failure.
 - 2.5.1 Role of renin-angiotensin system.
 - 2.5.2 Role of high plasma aldosterone.
 - 2.5.3 Identification of "additional Factor(s)" in sodium retention.
 - 2.5.4 Role of adrenergic system in sodium retention by the kidney.
 - 2.5.5 Role of local physical factors in sodium retention.
 - 2.5.6 Alterations in intrarenal hemodynamics.
 - 2.5.7 Role of ADH in cardiac failure.
 - 2.5.8 Role of other known humoral factors in cardiac failure (Bradykinin, prostaglandins, etc.).
 - 2.5.9 Animal models.
 - 2.5.10 Extra and intraluminal factors determining effect of load of water and electrolytes on their rate of tubular transports.
 - 2.5.11 Cellular mechanisms for water and electrolyte transport across the renal tubular epithelium.
 - 2.5.12 Afferent control mechanisms in the sodium retention of heart failure.
- 2.6 Partition of Extracellular Fluid Between Plasma and Interstitium.
 - 2.6.1 Control of capillary hydrostatic pressure.
 - 2.6.2 Control of plasma colloid osmotic pressure.
 - 2.6.3 Changes in capillary permeability.
 - 2.6.4 Tissue compliance, edema, lymph flow.
- 2.7 Regulation of Peripheral Circulation in Cardiac Failure.
 - 2.7.1 Development of techniques for measurement of blood flow to various organs.
 - 2.7.2 Regulation of the circulation in various animal models of heart failure.
 - 2.7.3 Regulation of arterial pressure and distribution of blood flow—neurogenic influences and reflexes.
 - 2.7.4 Regulation of arterial pressure and the distribution of blood flow—humoral influences.
 - 2.7.5 Regulation of arterial pressure and distribution of blood flow—intrinsic influences and autoregulation.
 - 2.7.6 The role of mineral metabolism and cations in the control of vascular reactivity in heart failure.
 - 2.7.7 Basic characteristics of vascular smooth muscle and other vascular tissues in heart failure.

- 2.7.8 Regulation of venous capacitance in heart failure.
- 2.7.9 The influence of environmental factors on the regulation of the circulation in heart failure.
- 2.7.10 The release of tissue factors which may regulate cardiac function in heart failure.
- 2.8 Effects of Lung on Cardiac Failure.
 - 2.8.1 Arterial hypoxemia.
 - 2.8.2 Pulmonary vascular disease as it affects cardiac function.
- 2.9 Effect of Cardiac Failure on the Lung.
 - 2.9.1 Basic regulation of fluid and protein exchange in the lung.
 - 2.9.2 Alveolar flooding and fluid clearance.
 - 2.9.3 Blood flow distribution in lung in congestion and edema.
 - 2.9.4 Regulation of breathing and distribution of ventilation.
 - 2.9.5 Pulmonary vascular resistance.
 - 2.9.6 Pleural effusion.
- 2.10 Effects of Cardiac Failure on the Microcirculation and Organ Nutrition.
 - 2.10.1 Intraorgan distribution of blood flow.
 - 2.10.2 Effects of reduction (and redistribution) of blood flow on blood-tissue transport.
 - 2.10.3 Influence of chronically reduced blood flow on intrinsic and extrinsic control of microcirculation.
 - 2.10.4 Cellular effects of reduced blood flow (metabolic and transport functions).
 - 2.10.5 Cellular effects of interstitial edema (metabolic and transport functions).
 - 2.10.6 Effects on other organ systems—blood.
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- 2.11 Drug Distribution and Disposition in Cardiac Failure.
 - 2.11.1 Drug distribution and disposition in cardiac failure.

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 - 3.1.1 Basic mechanisms of cardiac glycoside action—inotropic and metabolic effects.
 - 3.1.2 Basic mechanisms of cardiac glycoside action—arrhythmogenic effects.
 - 3.1.3 Approaches to digitalis toxicity.
 - 3.1.4 Altered sensitivity to cardiac glycosides.
 - 3.1.5 Interaction of cardiac glycosides with the autonomic nervous system.
 - 3.1.6 Interaction of cardiac glycosides with other drugs.
 - 3.1.7 Extracardiac effects of cardiac glycosides.
 - 3.1.8 Evaluation of effects of cardiac glycosides on cardiac performance.
 - 3.1.9 Evaluation of the effects of cardiac glycosides on the clinical outcome of cardiac failure.
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- 3.1.11 Design and evaluation of new cardiac glycosides and comparison with existing drugs.
- 3.1.12 Special problems in the use of cardiac glycosides in children.
- 3.1.13 Effects of cardiac glycosides on endocrine systems.
- 3.1.14 Physician education.
- 3.2 Inotropic Agents Other Than Cardiac Glycosides.
 - 3.2.1 Basic mechanisms—tissue selectivity.
 - 3.2.2 Basic mechanisms—contractibility.
 - 3.2.3 Pharmacokinetics.
 - 3.2.4 Effects on myocardial metabolism and coronary flow in normal and abnormal (e.g., ischemic) hearts.
 - 3.2.5 Effects on hemodynamics, regional flow and other organ functions.
 - 3.2.6 Development of new inotropic drugs.
- 3.3 Therapeutic Alteration of Impedance to Left Ventricular Outflow.
 - 3.3.1 Relation between aortic pressure and coronary blood flow and myocardial metabolism.
 - 3.3.2 Effects of changes in aortic impedance on left ventricular performance.
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 - 3.3.4 Regional distribution of flow induced by vasodilators.
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 - 3.4.1 Relation of filling pressure to cardiac function.
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 - 3.5.2 Effects of diuretics on intrarenal hormone release (renin, Bradykinin, prostaglandin, etc.) intrarenal hemodynamics and tubular action of extrarenal hormones (vasopressin, parathyroid hormone, etc.).
 - 3.5.3 Extrarenal effects of diuretic agents on cardiac function, vascular resistance and release of extrarenal hormones in presence and absence of alterations in water and electrolyte balance.
 - 3.5.4 Development and evaluation of new diuretic agents and vasopressin antagonists.
- 3.6 Therapy Directed to Altered Ventilatory Function.
 - 3.6.1 Artificial lung.
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 - 3.6.3 Improved methods for O₂ analysis.
 - 3.6.4 Prevention of hyperventilation.
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- 3.7.1 Research and development of better methods of physician education in the therapy of cardiac failure.**
- 3.7.2 Research and development of nonprofessional care—better use of health personnel for patient management and education.**

DATA SUMMARY FOR
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SHOCK



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- 1.1 Changes in the Microcirculation.
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 - 1.1.2 Distribution of flow within vascular network of organs and tissues.
 - 1.1.3 Diffusion of small molecules between blood and tissue.
 - 1.1.4 Effects of low blood flow on tissue oxygen and metabolism.
 - 1.1.5 Fluid balance: capillary pressure, capillary permeability, lymph flow.
 - 1.1.6 Methods of evaluating 1.1.1–1.1.5 in man.
- 1.2 Effects of Shock on the Kidney.
 - 1.2.1 Basic mechanisms of the control of renal blood flow and glomerula filtration.
 - 1.2.2 Basic mechanisms of acute renal failure resulting from shock.
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- 1.3 Effects of Shock on the Lung.
 - 1.3.1 Elucidation of general factors which contribute to the shock lung.
 - 1.3.2 Factors which regulate flow and its distribution within the lung in shock, including neural and humoral control.
 - 1.3.3 Pathophysiology of intravascular impairment of lung perfusion in shock including fat embolism.
 - 1.3.4 Alterations of fluid and protein exchange in the lung, including normal and abnormal lymphatic function, the alveolar capillary membranes and surfactant.
 - 1.3.5 Regulation of ventilation and distribution of ventilation in shock.
 - 1.3.6 Role of sepsis in shock lung.
- 1.4 Effects of Shock on Intestine, Pancreas and Liver.
 - 1.4.1 Effects of shock on splanchnic perfusion and its distribution.
 - 1.4.2 Effects of decreased splanchnic perfusion.
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- 1.5 Effects of Shock on the Heart.
 - 1.5.1 Techniques to evaluate cardiac function in shock.
 - 1.5.2 Evaluation of cardiac function in different forms of shock including metabolism, mechanics, electrophysiology, and coronary blood flow.
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- 1.6 Effects of Shock on the Blood.
 - 1.6.1 Significance of intravascular coagulation in the shock state.
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 - 1.6.3 Platelet and white cell aggregation in shock.
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 - 1.7.1 Metabolic response to tissue ischemia.



- 1.7.2 Metabolic response to shock including endocrine.
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- 1.7.4 Pathologic changes in tissues including structural and biochemical consequences of ischemia.
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 - 1.8.1 Significance of alterations of tone in shock (man and models).
 - 1.8.2 Methods to detect early increases of sympathetic tone in man.
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 - 1.9.1 Evaluation of significance in models and man.
 - 1.9.2 Chemical characterization and structure.
 - 1.9.3 Kinetic studies including formation-release-bioinactivations and excretion.
 - 1.9.4 Mechanisms of physiological action.

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 - 2.1.1 Prospective evaluation of patients with known coronary anatomy and other risk factors predictive of shock.
 - 2.1.2 Application of hemodynamic measures as a guide to early therapy.
 - 2.1.3 Systematic evaluation of treatment in early shock based on hemodynamic assessment.
 - 2.1.4 Development of new methods for estimating ventricular function and coronary blood flow in man including imaging and ultrasound.
 - 2.1.5 Research on validity of estimates of infarct size.
 - 2.1.6 Ethics of investigation in patients with shock.
 - 2.1.7 Centralized data collection and analysis.
- 2.2 Emergency Medical Care—Research and Development.
 - 2.2.1 Evaluation of early treatment on the development of severe shock.
 - 2.2.2 Evaluation of systems for early treatment of shock.
- 2.3 Inotropic Agents.
 - 2.3.1 Evaluation of inotropic agents including glycosides and glucogen in cardiogenic shock.
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- 2.4 Drugs Which Increase Peripheral Resistance in Shock.
 - 2.4.1 Role and consequences of vasoconstrictor therapy in different forms of shock.
- 2.5 Drugs Directly Causing Vasodilation.
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- 2.6 Alpha Adrenergic Blocking Agents.
 - 2.6.1 Controlled clinical studies.
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- 2.9 Prophylaxis and Therapy of Pulmonary Changes in Shock.
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 - 2.9.2 Evaluating need for assisting ventilation.
 - 2.9.3 Improved methods of assisting ventilation.
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 - 2.10.5 Development of the teams to conduct these studies.
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 - 2.11.1 Drug distribution and disposition in shock.



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NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME IV PANEL REPORTS

PART II

REPORT OF THE LUNG DISEASES PANEL



APRIL 6, 1973

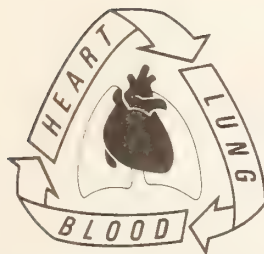
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F O R E W O R D

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423) requires that the National Heart and Lung Institute develop a plan for a National Heart, Blood Vessel, Lung and Blood Disease Program. The Institute established a committee of four panels to assist in the development of program plans for each of the four major program areas:

- Heart and Blood Vessel Diseases
- Lung Diseases
- Blood Diseases
- Blood Resources.

This report was prepared by the Lung Diseases Panel.



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P R E F A C E

The Lung Diseases Panel, appointed in September 1972, was charged to help develop a five-year plan responsive to the legislative requirements of the National Heart, Blood Vessel, Lung and Blood Act of 1972 and addressed to a national program against diseases of the lung. Reflecting the requirements of the Act, the Panel of ten physicians represented expertise in many areas: various diseases of the lung (obstructive, allergic, infectious and environmentally-induced diseases); pulmonary disorders of infancy and childhood as well as the adult; fundamental, clinical and applied research approaches; disciplines ranging from molecular biology, immunology, genetics and physiology to epidemiology; and problems associated with delivery of health care as well as of education, both professional and public.

To discharge its responsibilities, the Panel constituted itself into working groups with defined tasks relative to fifteen Problem Areas that it identified to be of prime importance in any program against respiratory diseases. The selection of these Problem Areas, presented in the sequence in which they appear in the Panel's report, is explained below:

1. The Normal Lung. Any insights into the processes by which pulmonary diseases develop, as well as how they can be properly diagnosed, effectively treated or prevented, must rest upon an understanding of the structure and function of the normal lung.



2. Environmental Respiratory Diseases. In our industrialized society, environmental respiratory diseases are both common and of mounting importance as a national health problem because we are continuously exposed to air pollutants and in some occupations to specific airborne noxious substances.
3. Emphysema and Chronic Bronchitis. These diseases are among the leading causes of death from respiratory diseases, a major cause of disability, and at present are irreversible by the time they are detected. Associated with cigarette smoking and, in certain cases of emphysema, with an inherited deficiency of an enzyme inhibitor, these diseases constitute a major and growing threat to national health.
4. Pediatric Obstructive Respiratory Diseases. These diseases (especially croup and bronchiolitis) are important because of their high morbidity, particularly in infants. Moreover, they may contribute to development of chronic obstructive lung disease in the adult, a possibility that requires further investigation.
5. Allergic Airway Disease. Asthma, the most common chronic pulmonary disease and the prototype of allergic airway disease, affects all age groups, can start in early childhood and last a lifetime, and contributes significantly to the national health burden by virtue of the high disability associated with this disorder.
6. Diffuse Interstitial Respiratory Diseases. These diseases encompass a variety of disorders which include acquired connective tissue diseases (such as rheumatoid arthritis) with pulmonary involvement, noninfectious pneumonitis resulting from radiation or drug reactions, and a large group of unknown cause, the idiopathic interstitial fibroses. Because these diseases collectively contribute significantly to disability from pulmonary diseases and because it is believed that in many instances they go undetected until they are irreversible, they constitute an important national health problem.
7. Infectious Respiratory Diseases. These diseases are the single most common cause of hospitalization as a consequence of respiratory disease. Infectious respiratory diseases contribute significantly to the overall problem of hospital-acquired infections, are frequently a cause

of death in patients admitted to hospitals for other diseases, and are implicated as a contributing factor to the severity of emphysema, asthma, pulmonary fibrosis, cystic fibrosis and other chronic respiratory disorders.

9. Sarcoid and Granulomatous Lung Diseases. These diseases are disorders that occur in early and middle adult life and hence have significant economic consequences. These diseases are often progressive and are more common in women and particularly common in blacks. They are of unknown cause, have eluded early diagnosis, and are sometimes not amenable to therapy.

10. Hypersensitivity Lung Diseases. Because they are caused by allergic reactions to specific organic dusts, hypersensitivity lung diseases are particularly common in specific environments and certain occupations. These chronic disabling diseases can at present be treated symptomatically but cannot be cured, and can only be prevented by avoiding exposure to the offending agent.

11. Pulmonary Vascular Diseases. These diseases (cor pulmonale, pulmonary hypertension and pulmonary edema) may arise from a variety of causes, but are frequently associated with pulmonary or cardiac disorders of high incidence and contribute significantly to the mortality from these diseases.

12. Respiratory Membrane Disease of the Newborn. This disease is usually associated with prematurity, affects about 40,000 newborn infants a year. As half of these will die unless treated by the most sophisticated techniques (which are not widely available), studies addressed to prevention of this disease are of greatest importance.

13. Cystic Fibrosis. This genetically determined disease is one of the main causes of chronic illness in children and young adults and accounts for most deaths from chronic pulmonary diseases in pediatric patients.

14. Acute and Chronic Respiratory Failure. Respiratory failure is associated with high morbidity and about 40 percent mortality. As the respiratory distress syndromes resulting from respiratory failure may be a consequence of severe accidental injury, it affects a large number of otherwise healthy persons--particularly young adults--as well as those with chronic debilitating pulmonary disease.

14. Extrapulmonary Manifestations of Respiratory Diseases. Respiratory diseases frequently produce abnormalities in cells and tissues of other organs, and thus commonly contribute to health problems.
15. Education in Lung Diseases. To successfully implement any program that is designed to modify the impact of respiratory diseases on public health, education of the scientist, clinician, allied health personnel and the lay public are all essential.

The notable absence of cancer of the lung from the Problem Areas considered by the Panel is not by oversight. Underlying problems of neoplastic disease are similar irrespective of the organ affected, therefore, no specific recommendations were developed in this area by the Panel.

For the substantive sections of its report, the Panel was subdivided into four Task Groups. A Consolidated Task Group formed by the Panel members functioning as a task group-of-the-whole had available the recently (October 1972) issued 243-page Report of the Task Force on Research in Respiratory Diseases, which identified the problems, research approaches and needs in eleven of the fifteen Problem Areas to be covered by the Lung Diseases Panel. This report served as the primary resource document for all Problem Areas except Pediatric Obstructive Respiratory Diseases, Hyaline Membrane Disease of the Newborn, Cystic Fibrosis and Extrapulmonary Manifestations of the Respiratory Diseases. This report was prepared by a 12-member Task Force involving 71 non-Task Force participants and an additional 105 consultants. Their report reflected a cross-section of professional expertise and opinion relative to respiratory diseases.

For three Problem Areas that were not specifically addressed by the Task Force on Research in Respiratory Diseases, the

Lung Diseases Panel constituted three additional Task Groups. Problem Area 4 was covered by a Task Group on Bronchiolitis and Childhood Obstructive Diseases; Problem Area 11 and the genetic aspects of Problem Area 3, by a Task Group on Cystic Fibrosis and Other Genetic Lung Diseases; and Problem Area 14 by a Task Group on Extrapulmonary Manifestations of Respiratory Diseases. Each Task Group included two Panel members, with one serving as chairman, augmented by a combined total of 12 physicians or biomedical consultants.

The appendices of this report list the members of the Lung Diseases Panel, of the Task Groups, and of the Task Force on Research in Respiratory Diseases. Grateful acknowledgement is also extended to the large number of biomedical scientists whose names appear in the Report of the Task Force on Research in Respiratory Diseases and who contributed indirectly to the work of the Lung Diseases Panel.

PART I

INTRODUCTION



PART I
INTRODUCTION

Respiratory diseases considered in the report account in aggregate for more than 126,000 deaths each year in the United States; for at least 181,000 man-years lost annually from the labor force; and an economic burden in excess of \$6.3 billion yearly, half of which is a consequence of the high morbidity from these disorders. As these data are based on health statistics for 1967--the latest year for which complete health data are available--it is abundantly clear that the figures are conservative estimates for diseases that are still increasing as national health problems. The magnitude of the health problems relative to specific diseases is identified in the sections on various Problem Areas.

In the face of this staggering health problem, there have been relatively limited resources for introducing significant changes. Moreover, medical science has been slow to bring to bear on the problems of respiratory diseases the



wealth of new knowledge and technology stemming from rapid advances in molecular biology, biochemistry and biophysics. And the field has failed to attract its share of bright, productive young scientists and physicians who must be looked to for future advances in any attack against respiratory diseases.

The Lung Diseases Panel has undertaken to identify the important problems still to be resolved and to suggest specific approaches to their solution. In the next section (Part II) of this report, each Problem Area is discussed in terms of the magnitude of the health problems consequent to the diseases under consideration and the current state of scientific knowledge about them. Recommendations are made for filling gaps in our present health programs and each problem is followed by a brief summary.

In Part III, the Panel summarizes the main recommendations for all Problem Areas. These recommendations are analyzed in Part IV in terms of the legislative requirements of the National Heart, Blood Vessel, Lung and Blood Act of 1972.

In reviewing the recommendations of each Problem Area, attention should also be given to the project areas identified by the Panel under each Problem Area. The specific proposed project areas are listed in Appendix C.



PART II

THE PROBLEMS AND PROPOSED PROGRAM



PART II

THE PROBLEMS AND PROPOSED PROGRAM

The following sections describe each of the 15 Problem Areas identified in Part I. With the exception of Problem Areas 1, The Normal Lung, and 15, Education in Lung Diseases, the section discussions are organized into five topics as follows:

- Introduction
- Magnitude of Problem
- Current State of Knowledge
- Recommendations
- Summary.

2.1 THE NORMAL LUNG

2.1.1 Introduction

During the past three decades much has been learned of the physiological behavior of the lung and its derangement in disease. The functional capacities of the lung and thorax that relate to ventilation, distribution of air and blood, diffusion of gases, pulmonary hemodynamics and mechanical characteristics of airways and alveoli have been quantified and interrelated. Although this information has provided clinically useful insights into the patterns of physiological dysfunction of the lung, these longstanding directions of research have not elucidated the precise basis of disease. Such derangement of respiratory function, while frequently life threatening, is usually the result, rather than the cause of pulmonary diseases. The missing links are knowledge and understanding of the alterations at the structural, cellular and molecular level which lead to altered pulmonary function. Virtually nothing is known of the manner in which pathogenic processes produce destruction and alteration of the architecture of the lung, or of the functions of the diverse classes of lung cells which are essential to its normal function and to its role in the physiological balance of the whole organism.

Study of the normal lung and the respiratory pathways is therefore essential for any progress in diagnosis, detection, management or treatment as well as rehabilitation. Such study provides the basis for a comparison of normal and abnormal structure and function, and thereby for evaluating the effectiveness of any modality of treatment.

it also provides the basis for the understanding of the pathogenesis of lung diseases by determining cellular and subcellular responses to varied pharmacologic agents as based upon the structural relationships within the tissue. It consequently provides the essential basis for the development of an effective preventive program. Research in this area is a sine qua non to progress at the clinical level. Nevertheless, the vast advances in molecular biology have not been adequately applied to the lung. Application of this new body of knowledge and its attendant techniques to the study of normal lung tissue is a prerequisite to the study of disease states. Consequently, study of the normal lung will support all forms of prevention, detection and diagnosis, treatment and management and rehabilitation.

2.1.2 Current State of Knowledge

Connective Tissue Structure of Lung Parenchyma and Airways

Although it has been known for many years that the lung is rich in collagen and elastin, chemical identification and quantification of these substances are at a preliminary stage of understanding, and the analytical methods used have been imprecise. The distinctive physical characteristics of these components contribute to the distensibility, collapsibility, and tensile strength of lung tissue and they form a geometric framework for the morphology of alveoli, airways, blood vessels, and their attendant cells.

In most forms of chronic airway obstructive diseases some destruction of lung parenchyma occurs, and, in pure emphysema, lung tissue dissolution is a primary process of unknown



etiology. Similarly, in fibrotic reactions of the lung, connective tissue growth and distortion of lung architecture is a prominent feature. But fundamental questions are still to be answered. These include:

- The quantities of connective tissue components in normal lungs, and differences in their quantitative distribution in various portions of the lung with age, sex and environmental influences.
- The amino acid composition of collagen and elastin in lung tissue, their chemical precursors, and their possible variations with age, sex, and environmental influence.
- Variations in quantity and amino acid composition of connective tissue components of the lung in diffuse pulmonary fibrosis and in various types of airway obstructive disease, particularly pulmonary emphysema and chronic bronchitis.
- The manner in which surface forces of the lining of alveoli and small airways interact with the mechanical characteristics of elastin and collagen within the interstitium, to produce observed physiological characteristics of stretch and collapse of the whole lung and within lung regions.
- The sites of synthesis and rates of synthesis and degradation of elastin and collagen in the normal and diseased lung.
- The in vivo balance and interactions between proteolytic enzymes with potential for structurally altering elastin and collagen at the molecular level, and the processes of synthesis, degradation, and destruction occurring normally and in lung disease. Answers to these questions are essential to an understanding of the pathogenesis of obstructive airway disease, but are equally important for elucidating the mechanisms of injury and repair in other forms of pulmonary disease, such as diffuse interstitial fibrotic reactions of the lung, bronchiectasis, asthma, respiratory distress syndrome of the newborn, and cystic fibrosis.



Pulmonary tissue substrates should be more fully investigated. While it is known that alveolar walls consist of at least four components--collagen, basement membrane substance, elastic fibers, and other protein components (consisting in part of glycoproteins)--their proportions and specific amino acid composition and structural arrangements are undefined. In vivo investigation of their rate of synthesis and turnover, by means of radioactive proline and lysine, should be encouraged. Clinical studies in which urinary connective tissue components are used to define altered turnover rates of connective tissue in pulmonary disease should be explored, as they are potentially useful methods for screening and for an understanding of pathogenesis.

The normal quantities and types of protein components of alveolar walls, as well as bronchi and bronchioles, in the various portions of the lung should be studied. The constancy, as well as inconstancies of protein composition and structure in the normal lung, and variations with age, sex, and environment may be important for understanding patterns of pulmonary destruction in obstructive lung disease. Recent work has corroborated the increase, with age, of elastin in the pleura as compared with the parenchyma, and has shown similar changes in amino acid composition of elastins in aorta and lung, but the physiologic or pathogenetic consequences of such changes with age are unknown.

Chemical Mechanisms of Pulmonary Injury

Functional disturbances of the lung in various types of chronic lung disease may be due to irreversible structural

alterations in various tissues of the lung, but we have no clear notion of the mechanisms which initiate and perpetuate them. There may be many types of lung tissue injury and these may depend upon structural differences in, for example, alveolar tissue as compared with the walls of bronchi or blood vessels.

Within the last decade a potential mechanism of lung injury has been identified, as more has been learned about pulmonary emphysema associated with inborn α_1 -antitrypsin-inhibitor deficiency in humans. Imbalances between proteolytic activity, and its control or inhibition may have profound implications as a generalized mechanism of lung injury in other pulmonary pathological states, such as those related to infection, air pollution or the respiratory distress syndrome of the newborn. Key questions with regard to this mechanism in the pathogenesis of obstructive lung disease include:

- Are predispositions to lung disease due to overproduction of proteolytic enzymes, or qualitative differences in chemical potency, or release of these enzymes in individuals who are prone to chronic lung disease? Or, conceivably, do the initiating causes of lung injury involve environmental toxins which may induce changes in the production or the type of proteolytic agents in circulating polymorphonuclear leukocytes or alveolar macrophages?
- What are the early and late structural effects on collagen, elastin, and glycoproteins of these agents? Do different susceptibilities to reactions with proteolytic enzymes exist with regard to age, sex, ethnic background and environments?
- What are the chemical characteristics of proteases having access to the lung under normal and certain pathological circumstances?



- What are the characteristics of circulating leukocytes and the alveolar macrophage with respect to population, turnover, and migration to the lung from the bone marrow?
- What are the mechanisms by which lysosomes release proteolytic enzymes?
- What are the chemical interactions between the gaseous and solid products of smoking and lysosomal function of the macrophages?

Structure, Synthesis and Physical Characteristics of Bronchial Mucus

Increased production of bronchial mucus and an inability to clear the airways of secretions are critical pathological factors in many common diseases of the lungs such as chronic bronchitis, cystic fibrosis, asthma, acute respiratory distress syndrome and infectious pneumonitis. Effective treatment of these diseases requires an ability to control the viscosity, rate of production and methods of elimination of mucus. There is little information at present on these factors. Further work on the fundamental chemistry and pharmacology of mucus production is essential to the improved potential for dealing with these crucial aspects of the pathogenesis of lung diseases.

Bronchial secretions consist almost entirely of water which is so organized in the structure that it does not flow freely through the gel. The organization of water in the gel structure of bronchial secretions is one of the important factors affecting the consistency of secretions. Therefore, more information is required on how chemical agents may change sputum consistency by altering



the hydrogen bonding of the water incorporated in the gel. Present information indicates that the gel structure of bronchial secretions includes a basic protein and two types of glycoprotein which are cross-linked to one another by disulfide bonds. The disulfide bonds can be disrupted by sulfhydryl agents such as N-acetylcysteine or dithiothreitol which in turn alter the consistency of secretions. However, there is no information on where the disulfide cross-linkage takes place, whether before or after secretion, and by what chemical process.

Similarly, little is known of the factors which control elasticity and viscosity of secretions, factors which are not mutually dependent and can be influenced separately. Of particular relevance is the effect of purulence on the physical properties of sputum and the effect of atmospheric pollutants such as tobacco smoke on the production and chemical composition of bronchial secretions. Information is also needed on the specific glycoproteins which provide a skeletal framework for the gels of bronchial secretions.

Phospholipid and Protein Synthesis by the Lung

The potential of specific cells of the lung for phospholipid and protein synthesis and degradation is substantially unknown. This lack of knowledge is especially relevant to the pathogenesis of common pulmonary diseases:

- The normal composition of surface active material is unknown, although it is generally agreed that dipalmitoyl lecithin is an essential component. Since dipalmitoyl lecithin occurs not only in surfactant but also in membranes, methods to detect

and quantify surfactant, which depend upon analysis of the concentration of dipalmitoyl lecithin alone, may be misleading. Better methods should be sought.

- Lack of knowledge of the normal structure of surfactant prevents thorough understanding of its alterations in disease, and of the control or prevention of these alterations by physiological conditions in the lung.
- Basic information is required on the pathways and mechanisms by which surfactant is dissipated or removed from alveoli.

Glycoprotein Structure of the Lung

Glycoprotein structure of basement membrane varies greatly in different organs; for example, lung basement membrane resembles that of the choroid plexus of the central nervous system more than the basement membrane of the glomerulus or Descemet's membrane of the eye. The basement membrane of the lung has very special characteristics with respect to diffusion of respiratory gases or electrolytes and environmental gases. The biochemical structure of normal lung basement membrane with respect to its permeability characteristics has not been defined in man, and we have no information on its changes with advancing age or disease.

Chemical characterization of lung basement membrane is a necessary first step to understanding the immune potential in certain diseases of the lung which make the basement membrane a target for pathogenic processes, such as in Goodpasture's syndrome.

In this regard experimental models providing embryonic tissues may be used to define the components and their origin in the basement membrane. Similarly, tissue culture preparations of whole lungs or of cell lines of pulmonary origin would be experimentally useful. Such studies may be of fundamental importance in understanding the function, structural components and mechanisms of disease of the basement membrane of the lung in the mature organ.

Exchange and Transport Functions of the Lungs

The lungs serve as the interface for the entry of oxygen into the tissues and for the removal of carbon dioxide. Preservation of the alveolar structures which provide for the contact between the gas phase and the blood is essential if the exchange and transport functions of the lungs are to be carried out efficiently. Information bearing on the composition and other characteristics of the cell and connective tissue constituents of the alveolar structures obtained by the methods of molecular biology must be complemented by studies of the compartments of the lung tissues and by the characterization of membranes or barriers which provide the compartmentation into the vascular, interstitial and cellular components. Thus, one of the most common problems encountered clinically is pulmonary edema. This is characterized by an increased fluid content in the lungs. How does this fluid accumulate? Is it solely because the rate of fluid entry is increased? Is there a failure of lymphatic drainage to accommodate the increase? Is the composition of the excess fluid the same as a protein-free filtrate of plasma? Does its composition differ from that of the interstitial fluid

normally present? Is all the fluid interstitial? Or is there some increase in cell volume in pulmonary edema (endothelial, interstitial, epithelial or all)? Are the characteristics of the barriers, both endothelial and epithelial, the same in pulmonary edema as normally? Barriers can best be characterized by means of their thermodynamic coefficients of permeability, filtration and solute reflection. Some data are available from experiments and studies in special preparations bearing on these matters but the scope is quite limited, and the significance and applicability of the results is still somewhat uncertain. For example, we are still ignorant of the manner in which water and other substances cross the endothelial barrier. The relative importance of various potential pathways (such as intercellular pores, transcellular passage, protein or aqueous channels as opposed to lipid portions of solubility membranes) has not been determined in the normal lung. These parameters of the normal lung must be defined before it is possible to draw meaningful deductions from studies in pulmonary edema, in the shock lung or in pulmonary infections.

In a similar manner, studies of the overall function of the lungs of the more conventional respiratory physiology type would be complementary to these studies of the barrier characteristics. With results of both types of studies available, it should be possible to determine more precisely the extent to which gas and other exchanges occur across other vessels than the capillaries in health and in disease. The relative roles of convection of bulk flow and diffusion in the gas phase need to be determined more accurately not only in the normal lung but also in



disease states such as the pneumoconioses, emphysema and chronic bronchitis and various bacterial infections.

Studies of the normal lung must also include approaches which have become more clearly indicated in the light of the disturbances which occur in certain disease states. Thus, with a greater accuracy in assessing pulmonary functions such as ventilation, flow rates, compliance, etc., the more readily will it be possible to detect significant deviations and to provide earlier detection of disease. To this end, improved instrumentation is required and much more sophisticated techniques must be developed to permit measurement of, for example, pulmonary artery pressure, extravascular lung water, and right ventricular hypertrophy.

2.1.3 Recommendations

Firstly, it is suggested that increased knowledge should be sought of normal lung development, its biochemical maturation and the histologic changes in aging. This can be achieved by determination of defined constituents in normal and abnormal development. Growth and aging of the lung parenchyma, the blood vessels and lymphatics, the factors associated in aging, and the establishment of normal values for lung function with aging should be studied. Studies are also needed in embryology and teratology of the lung. The aging of the lung should be studied in relation to such factors as free radicals and physical stresses.

It will be important to use newer ultrastructural and biophysical techniques, which are required for understanding

of how lung structure and function are altered in disease, by providing background data on the normal development of the lung. The revolution in cell biology has enabled the framing of a new cell atlas. The application of these techniques to the lung should include use of scanning and transmission electron microscopy, and such other new techniques as freeze-etching, and high-voltage electron microscopy.

Studies of the morphometry of lung tissues should permit consideration of the lung as an organ in terms of its biophysical responses.

It will also be necessary to analyze the chemical structure and physical properties of individual lung components. This should be accompanied by chemical dissection of the lungs themselves, thus permitting studies of discrete materials obtained from the normal lung. The biochemical studies should be correlated with the physical properties of the isolated material in order to compare this with diseased tissues. This can be performed by analysis of the growth, or composition, of the lung. This should be followed by the study of the tissue including collagen, reticulin, elastin, etc., and especially by their isolation and characterization of the alveolar wall, the basement membranes and the fibrous proteins which compose them. Efforts should be made to characterize and analyze the influence of lung substances upon the elasticity, strength and compressibility of the organ. Studies should be concerned with the changes occurring with maturation upon the composition and function of lung surfactant.

It will also be important to explore the cell and molecular biology of uniform cell populations from human lung. These cell populations need to be isolated and cultured. Once alveolar parenchymal cells, bronchial epithelial cells, etc., are obtained in pure yield, their metabolism, energy requirements and discrete functions can be analyzed. This is mandatory for understanding their derangement in disease. Thus the following projects should carry significant priorities:

- Separation of uniform populations from the lung
- The growth of diploid long-term cell lines from these populations
- Classical subcellular fractionation of uniform cells including the obtaining of mitochondria, lysosomes, etc.
- Studies of energy metabolism
- Studies of transcription and translation
- Studies of prostaglandin and lipid biosynthesis

It will also be necessary to study the responses of each of these above parameters to pharmacological manipulation, especially those at present used in lung disease. The genetic control of cell functions with respect to the above parameters should also be studied. Moreover, as before, it is important to study the changes of maturation of these cells.

The transport and membrane systems of the lung should be studied, since a major function of the lung is to provide a means for gas exchange. Our understanding of this



function at the moment is still imperfect and the objective will be to increase our knowledge of this function. Studies of transport function should lead to the development of the essential understanding of how the lung breathes. In order to do this it will be important to characterize exchange and transport barriers in terms of irreversible thermodynamics by measuring reflection coefficients, permeability, and filtration coefficients. It will also be important to characterize membrane functions of individual cell lines obtained from the lung with respect to the above and to determine the effects of physical and chemical modifications of their internal and external environments upon the above characteristics.

Studies of membrane gas transport should include studies of the effects of changes in pH upon the kinetics of oxygen release and the controls exerted by such chemical mediators as 2, 3-diphosphoglycerate (DPG) upon these. It is necessary, moreover, to study carbon dioxide with respect to its effect on intracellular oxidation-reduction potentials and carbamino compounds and to study the exchange of inert and anesthetic gases across the lung membranes.

Finally, it will be important to determine the relative roles of convection and diffusion in airways and tissues, as well as to study the barrier and membrane characteristics with growth and maturation as before.

It should also be of interest to study respiratory secretions, because these provide the basis for understanding disordered functions in many diseases. These secretions

provide a basis for the removal of foreign materials, protection of mucosal layers, and residuals of phagocytic activity. The process is analogous to the secretory mechanisms in other exocytic cells and can be studied by similar biochemical and ultrastructural techniques. Study of the biochemistry of glycoproteins should begin with the synthesis of glycoproteins, by studies of glycosyl transferases or other enzymes of the golgi apparatus, and by analysis of the physiocochemical characteristics of the glycoproteins of mucus. It will also be necessary to investigate the flow characteristics of mucus, the relationship of fluid to particulates, etc. Underlying all, studies should be directed towards the basic cell biology of mucus packaging and extrusion.

It will be necessary to investigate ciliary structure and function in order to develop knowledge of these with respect to lung hygiene and host defenses. Cilia are composed of microtubule proteins and their function and structure can be analyzed by the techniques used to study cilia from other sources in lower species. Thus, investigation should be directed towards study of the cell biology of ciliated epithelium. A relationship between centrioles, microtubules, and tubulin should be established using the techniques of immunofluorescence, biochemical analysis, and isolation. Corollary studies should be directed towards the physiologic controls of the integrity of cilia and of their activity. These are realized by enzymes such as adenylyclase, protein kinases and such cofactors as calcium ions, other cyclic nucleotides, etc., as well as by physical irritability, stimuli secretion, etc. Ciliary response to cytochalasin or colchicine in relation to



prostaglandins and autonomic agonists also deserve attention.

A number of classical areas of pulmonary physiology require continued study. Such areas include studies of the mechanical properties of the ventilatory apparatus and the pulmonary vascular bed. In these, bioengineering collaboration could provide new insights. The coupling of mechanical events to the neurophysiological regulation of ventilation is likewise an important area. Continued investigation concerning the relationship of mechanics to pulmonary gas exchange should be supported.

2.1.4 Summary

The significance for lung diseases of studies on the normal lung is overwhelming and must not be underemphasized. In the absence of the kind of background information suggested above, all further studies in etiology and pathogenesis are not fully useful because their grounding in basic cellular biology will not become apparent. Moreover, progress against disease (as evidenced by recent progress in cancer chemotherapy) cannot be expected unless clinical observations are related to basic biochemical mechanisms in lung tissue. These can only be accomplished after a thorough understanding of:

- Cell Biology
- Biochemistry
- Immunology

- Molecular biology and
- Physiology.

It must therefore be emphasized that this section is the key to all the other project areas and approaches, because without significant investment in this area of research and development the clinical observations will be based upon an uncertain foundation.



2.2 ENVIRONMENTAL RESPIRATORY DISEASES

2.2.1 Introduction

This group of diseases results from a variety of chemical and biological exposures. Most simply they may be categorized into exposures related to general ambient air, occupation and to tobacco smoking. In addition there are effects of barometric pressure, temperature, humidity and ionizing radiation. The various factors may act singly or in conjunction with other agents either synergistically or additively. In most instances the extent of this interaction is not known.

It should also be emphasized that the lung is one of the major portals of entry of a variety of compounds that in transit may cause damage not only to the lungs, but also to other organs or systems in the body. For example, lead can affect the brain, red blood cells, or gastrointestinal tract, and mercury, manganese, and carbon disulfide can affect the brain.

2.2.2 Magnitude of Problem

With the growth and increasing complexity of industry, many working people are exposed to dust, fumes and vapors which may cause lung disease. The number of people affected is very large, albeit incompletely recorded. Recent estimates suggest that more than 500,000 workers are exposed to irritant gases, 1,000,000 to silica, 250,000 to asbestos, and there are 200,000 coal miners and 500,000 cotton textile workers in this country.

The increasing technological complexity of industry has introduced and will continue to introduce into the industrial environment a variety of exogenous agents implicated in the etiology of occupational lung disease. Moreover, the time-lag in identifying toxic agents is such that there is strong suspicion that many agents have not yet been identified. The hazard of exposure to cotton textile dust was established in this country only in the past decade; bentonite (long assumed to be an "inert" dust) has now been shown to produce severe lung disease among those mining it in Wyoming; and the biological potential of a widely used industrial chemical, bis-chloromethyl ether, and of fine fibrous glass has only recently been reported.

The high incidence and serious nature of respiratory disease among cigarette smokers has been amply documented. As stated in the Surgeon General's first report: "Cigarette smoking is the most important of the causes of chronic bronchitis in the United States and increases the risk of dying from chronic bronchitis." Some measure of the magnitude of the problem of respiratory diseases from smoking may be inferred from data from the National Center for Health Statistics: 69.3 percent of adult males and 42.8 percent of adult females had a history of regular cigarette smoking in 1970. The Center has also recorded that emphysema afflicts approximately one percent (or 2,000,000 persons) of our total adult population, while bronchitis is found three times as frequently. Though well known, this information has not influenced the smoking habits of the population.



Data that characterize and define the nature and extent of chronic lung disease associated with community air pollution are meager and uncertain. Where data on community air pollution are available their interpretation is unclear unless the concomitant effects of smoking are taken into account.

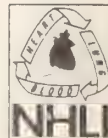
2.2.3 Current State of Knowledge

Current mechanisms for obtaining epidemiological data need to be improved: Former studies have been concerned mainly with prevalence rates, have long time-lags, usually identify only gross disease, and have not employed available field methods for early detection in the population studied.

There are virtually no firm data relevant to dose response for any single etiologic agent or any combination of agents whether they are occupational, environmental, or endogenous. These problems, although serious, are amenable to solution.

To minimize time-lags in the future, it is important to initiate epidemiologic studies of working populations exposed to substances of known toxicity but for which little or no epidemiologic data are available.

Little is known of the submicroscopic particulate burden of community air, despite its potential importance. This area offers an exceedingly important new frontier for research, with relevance not only to industrial lung disease, but to atmospheric pollution, as well. It may turn out that particles visible by light microscopy play a relatively



minor role in human disease. Submicron particles almost invariably accompany them, and may have much greater pathogenic significance. This is largely unstudied. In smoking, for example, such fine particles may exert their effect directly, by virtue of their specific chemical or physiochemical nature or indirectly by acting as carriers for gaseous and other substance, or by interacting with other elements in cigarette smoke. An example of the potential importance of this largely unexplored field is that cigarette filters designed for gaseous components may be ineffective for microparticles.

Evidence has already established that interactions of two or more factors greatly increase the risk of occupational lung cancer and pneumoconiosis. It is possible that much occupational lung disease, and environmental lung disease, will not be indentified or properly studied by investigating single factors. It may be that many industrial lung diseases would not occur except for the effect of two or more agents. In such circumstances, it could be practical to focus on the elimination of the one agent least difficult to control. Such knowledge would be immensely useful.

In most instances, dose-response relationships must be derived from research in occupational circumstances, especially when investigating diseases with a long lapse between exposure and onset of the disease. Nevertheless, the results will be applicable to respiratory disease which might be associated with atmospheric pollution in the general community. While there can be no automatic carryover of occupational "threshold levels" to circumstances of community exposure, the data will have some relevance to the general population.



While epidemiologic investigations may define problems, provide clues about etiologic factors, and lead to immediate preventive measures and surveillance that will have long-range impact on therapy and prevention of environmental disease, such approaches should also include studies of the cellular dynamics, physiology of the airways and vascular bed, and neural control of pulmonary function. There has been little work concerning air pollutants, occupational exposure, and cigarette smoking in these areas.

2.2.4 Recommendations

It is important to initiate epidemiologic studies of populations whose lungs are exposed to toxic substances. Industry-wide surveys would be in order for the chemical industry, petroleum refineries, shipyards, and commercial agriculture. Rapidly developing technology carries with it the possibility that new agents capable of causing occupational lung disease will be widely introduced, over rather short time-spans. It is important to detect such substances early. Appropriate physiological studies can be useful, especially if populations newly exposed can be defined and followed. Laboratory studies of suspect agents can include a variety of test systems. The least that can be expected from such an approach is documentation of a presumed innocuous nature. Early detection of important pulmonary disease hazard is important. We should not depend on the human test systems involving industrial workers as "nature's clinical experiment." The long time-lag sometimes inherent in such an approach is no longer acceptable. Therefore, before employees are exposed to



the inhalation of potentially toxic substances, studies should be used to determine their relative safety.

Cigarette smoking and air pollution epidemiologic investigations have tended to be cross-sectional or point-prevalence studies, with little recorded concerning the natural history of respiratory disease at various levels of exposure. There is a definite need to extend these into prospective studies.

Research is needed to determine the submicroscopic particulate burden of community air. This is mainly an unstudied area despite its potential importance. Sources of submicroscopic particulate matter in community air include cigarette smoke and industrial air pollutants.

Information is needed concerning the mechanism of cigarette smoking damage and community air pollution damage. Studies should include clearing mechanisms, ciliary action, and quantitative studies of bronchial cellular change. What have not been looked at carefully have been the determinants of individual response, including metabolism of cigarette smoke and air pollution products, enzyme effects, and variations in tissue repair. Are there inborn metabolic differences which result in one person developing serious pulmonary disease, and another showing very little? Appropriate genetic and metabolic studies of siblings might provide useful information in this regard.

In addition to cigarette smoking there are exposures to physical factors (such as high or low temperatures, dry or wet atmospheres, radiation of several types), physiological states (such as pregnancy, advanced age, and



poor nutrition). Infection may be important, as may be altered metabolic or genetic patterns.

Allergic respiratory disease is an important area for basic investigation. Investigation of unusual allergens which may affect immune status is a virtually unexplored field of considerable clinical and theoretical importance. Advances in this area may assist us to identify hyperreactors to a number of industrially important substances, such as toluene diisocyanate (TDI), cotton dust, molds (Farmer's Lung, Bagassosis), causes of a variety of forms of extrinsic allergic alveolitis, and industrial enzymes. Immunological research addressed to the interaction of inhaled materials, connective tissue, pulmonary cells, and the lymphatic and vascular systems in the lung also holds promise.

The discovery that, in some individuals, deficiency of serum α_1 -antitrypsin is associated with the development of disabling or fatal emphysema opened a fertile field for investigation of the metabolic status of individuals and their reactions to respiratory irritants. Such research could extend far beyond enzymes and should include chemical mediator substances. Clarification of the role of such substances in byssinosis and asthma will have wide application in many types of environmental lung disease.

An important area for research is investigation of younger age groups, particularly children. Far too many studies on chronic lung disease have dealt only with older age groups, where the disease is usually irreversible and medical treatment of relatively little benefit. Studies of



children will provide information on whether air pollution in childhood may be the starting point for environmental lung disease and for continuation and progression of such disease in later life. The study of the natural history of pulmonary disease associated with community air pollution should properly begin in childhood, and should also take into account such additional factors as housing, nutrition, and respiratory infections.

There has been little research on ameliorating or reversing the effects of occupational lung disease, or preventing its progression after removal from additional exposure. New leads have appeared and should be vigorously exploited; it has been demonstrated that at least one substance (polypyridien-N-oxide) can prevent silica fibrogenesis in the experimental animal even when administered after dust exposure. There is reason to believe that a variety of substances can affect the biological properties of pathogenic dust, at least for in vitro test systems. The promise of these observations should be vigorously explored and additional research stimulated on approaches to neutralize lung dust in vivo.

The important issue of rehabilitation is discussed in this Problem Area, and the other Problem Areas will refer back to this discussion. Rehabilitation is approached in a uniform fashion for all Problem Areas. The reason for this is that rehabilitation is felt to be applicable to all chronic or debilitating lung disease in a standardized fashion, and the overall programs will have little variance from Problem Area to Problem Area. However, Problem Area 11, Hyaline Membrane Disease of the Newborn, and Problem Area 13,

Acute and Chronic Respiratory Failure, discuss several rehabilitation projects beyond the standard programs outlined below.

In order to obtain a firm base of understanding, critical evaluation of present rehabilitative regimens should be conducted. These clinical studies should be prospective and controlled, and the following regimens should be examined: role of physical therapy, occupational therapy, exercise and psychological support. Inherent in these studies will be the evaluation of existing interdisciplinary programs that integrate the above regimens.

Following the above studies, planning and development of models of comprehensive rehabilitation programs should be conducted. These models should provide the experimental setting for testing both old and new regimens and determining how they interact in an interdisciplinary framework to produce efficacious comprehensive rehabilitation programs. Following these experiments, effective comprehensive rehabilitation programs can be established on a sound and well-tested basis.

2.2.5 Summary

Environmental respiratory diseases inflict a great toll on our population. Toxic industrial air pollutants, community air pollution, and cigarette smoking are the main causes of this significant morbidity and mortality. With the increasing level of air pollution it is vital to identify through epidemiologic and scientific study the relationship between community air pollution and respiratory



disease. This data and understanding will enable us to develop preventive, diagnostic, treatment, and rehabilitative skills in dealing with this problem.

Much more should be learned concerning cigarette smoking, both epidemiologically and in terms of mechanism of damage. With this information more effective means of prevention can be developed, and at the minimum, efficacious means of diagnosis, treatment and rehabilitation as interim measures can be developed.

Finally, more knowledge and understanding is needed concerning toxic industrial air pollutants, the submicroscopic particulate burden of community air, exposure to varying physical factors, response to air pollutants as allergens, and childhood environmental respiratory disease.



EMPHYSEMA AND CHRONIC BRONCHITIS

2.3.1 Introduction

Although emphysema and chronic bronchitis have distinctly different pathologic expressions, they are frequently referred to as chronic obstructive lung disease. This term reflects the fact that most patients with these diseases are recognized when the process is moderately or far advanced. At this stage, patients with either disease complain of similar symptoms, i.e., cough and breathlessness have similar aberrations of the commonly measured parameters of clinical pulmonary physiology; almost always have a history of prolonged cigarette smoking; and may have pathologic evidence of both diseases. It is reasonable to assume that the future direction for scientific investigations can be discussed for both diseases although eventually as our knowledge increases we may recognize more dissimilarities between the two and plot separate strategies for scientific inquiry.

2.3.2 Magnitude of Problem

Death rates in the United States from respiratory disease have increased since 1958 only for malignancies, bronchitis (unqualified), chronic bronchitis, and emphysema. In other categories, the death rate has declined or remained constant. For malignancy, the death rate between 1958 and 1967 increased by 44 percent; for unqualified and chronic bronchitis by 80 percent; and for emphysema by 172 percent. The leading causes of death from respiratory disease are malignancy and pneumonia, with death rates in 1967 of 29.3



and 28.0 per 100,000 respectively. For emphysema, another leading cause of respiratory death, the rate in 1967 was 10.6 per 100,000.

Since emphysema and chronic bronchitis are thought to predispose to pneumonia, the actual number of deaths related to these diseases may be much higher. The exact numbers are not known because data on deaths from pneumonia are not subdivided into predisposing causes. Nonetheless, it is reasonable to assume that many deaths due to pneumonia would not have occurred if the patient had not suffered from underlying chronic obstructive lung disease.

The socioeconomic impact of these diseases is extremely difficult to assess. The most complete data available are from 1967. The accuracy of mortality and morbidity statistics depends upon the accuracy of diagnosis which has been steadily improving over the years and may account for some of the increased incidence. Based on such limited statistical data, estimates of socio-economic costs are subject to very large errors.

For 1967, the estimated cost of morbidity and mortality due to (1) emphysema, (2) chronic and unqualified bronchitis, and (3) bronchiectasis was \$1.8 billion. Of this amount, the morbidity costs were \$1.2 billion, including \$655 million that represented loss of earnings. The estimated cost of all respiratory diseases, excluding cancer, was \$6.3 billion for 1967. It is believed that about one-third of this total was due to underlying bronchitis and emphysema. In terms of man-years lost due to lung disease in 1967, it is estimated that chronic bronchitis and emphysema account for 100,000 man-years. Thus, these diseases



represent, in terms of both incidence and cost, the most important public health respiratory problems in the United States, and they are increasing at a most rapid and alarming rate as major causes of death.

2.3.3 Current State of Knowledge

Natural History

By the time they develop breathlessness or other symptoms, patients with chronic bronchitis or emphysema are at a comparatively advanced stage of their disease. Current therapeutic measures appear useful for acute exacerbations, but there is evidence that such treatment does not delay deterioration of ventilatory impairment or the development of respiratory failure and cor pulmonale. Hence most physicians feel that they can only offer symptomatic relief for patients after they develop clinically recognizable disease. In the absence of an unforeseen breakthrough, there seems to be little gained by investigation of advanced disease using traditional methods. Study of end-stage disease leads to confusion as to what is cause and what is effect.

Much less is known about the earlier stages of these diseases, although basic physiological studies in the last decade have now opened the way to such studies. The problem has been to establish the presence of impaired function in the peripheral airways within which obstruction develops from a variety of causes. Normally, peripheral airways contribute little to total pulmonary resistance so that considerable obstruction can be present within them with

little impairment of lung function. As described below, however, newly applied tests for lung function have been found to be sensitive indicators of peripheral airway abnormality at a stage when routine tests of lung function are normal. Within the past two years, the use of these tests has shown that a substantial proportion of cigarette smokers are abnormal when compared to a control group of nonsmokers.

In assessing abnormalities in "early" peripheral airway obstruction, a major problem is to define "normal" and "abnormal." Most normal values for routine tests of lung function include measurements in asymptomatic smokers as well as nonsmokers. Thus, when normal values of routine tests become defined in a nonsmoking population, the sensitivity tests of peripheral airway obstruction may be improved.

The technology is probably adequate for defining the natural history of chronic obstructive lung disease in its earlier stages. Such studies are urgently need to answer the following important questions:

- The first of these is reversibility. There is evidence that cessation of smoking may reverse some of the early abnormalities of lung function. This suggests that some of the earlier manifestations of these diseases are reversible, and others are not.
- The second question concerns the long-term significance of abnormalities found in these sensitive tests of lung function. It is unknown whether, in the future, patients with advanced irreversible airways obstruction will come from a population of smokers with evidence of abnormalities in



peripheral airways. The answer to this question will require long-term prospective studies.

- The third question is whether or not sensitive function tests can be used to define a group at high risk to develop chronic irreversible airways construction. This will also require short-term and long-term prospective studies.

Etiology

Numerous factors, both exogenous and endogenous, are implicated in the etiology of these forms of airway disease. It is quite clear that cigarette smoking is the most important exogenous factor in development of both chronic bronchitis and emphysema. Although air pollution also plays a role, it is secondary. While it is clear that almost all patients with end-stage obstructive lung disease are smokers, the fact that not all smokers develop severe pulmonary dysfunction indicates the importance of other factors in etiology. There is a sex difference in susceptibility to development of chronic irreversible airways obstruction but why females are less susceptible is unknown and largely unexplored. In this regard, the finding that progesterone protects against the development of papain-induced emphysema in experimental animals is of considerable interest. The role of previous airway disease (such as bronchiolitis in childhood and repeated upper respiratory tract infections), in the etiology and pathogenesis of chronic airway disease requires definition.

Inherited genetic defects can predispose to both the development of peripheral airways obstruction (cystic fibrosis) and to emphysema (α_1 -antitrypsin deficiency). Within the last decade a potential mechanism of lung

injury has been identified, as more has been learned about pulmonary emphysema associated with inborn α_1 -antitrypsin-inhibitor deficiency in humans.

It is suggested by several studies that the mode of inheritance for α_1 -antitrypsin deficiency is autosomal recessive, and thus the expected incidence is approximately 1:1000. While it is recognized that the majority of individuals with chronic obstructive lung disease have a normal protease inhibitor genotype, the incidence of obstructive lung disease and emphysema in individuals who have the genotype associated with severely deficient α_1 -antitrypsin may be as high as 60 percent in those below age 60. This genetic association might play an important role in the interplay of genetic and acquired or environmental factors in the production of obstructive lung disease and focuses on the possible role of proteolytic mechanisms and their inhibition as a basis for pulmonary injury.

More than 13 molecular variants of the antitrypsin molecule have been discovered in serums from different individuals. Some of these variants are definitely known to be associated with severe or moderately severe deficiencies of antitrypsin activity in the blood and to predispose to pulmonary emphysema. Others are not so clearly defined in this regard and their clinical significance is uncertain.

Several studies suggest that avoidance of smoking may slow the progress of lung damage in protease inhibitor deficiency. Likewise, avoidance of industrial and other environmental pollutants or infection may be important. Introduction of increases of serum α_1 -antitrypsin to

intermediate or normal levels could prevent progressive lung damage.

Little is known of other genetic abnormalities which predispose to airways obstruction and emphysema, although familial chronic obstructive lung disease without cystic fibrosis or α_1 -antitrypsin deficiency has been described. A virtually unexplored area of research is whether genetically and/or environmentally determined "normal" differences in structure and function (such as the normal variability in the ventilatory response to CO_2 and maximum expiratory flow rates) predisposes to the development of disease. Although several hypotheses have been proposed as to why some subjects with airway disease develop respiratory failure, while others do not, this fundamental question remains unanswered.

Pathophysiology

The pathophysiology of airways obstruction and emphysema in their advanced stages has been described in great detail from the point of view of lung mechanics, ventilation distribution, gas exchange, diffusion and pulmonary circulation. Suitable tests have been devised to readily detect airway obstruction when it is moderately advanced and loss of elastic recoil, which is generally regarded as a hallmark of emphysema. With intelligent interpretation of routine function tests it is possible to predict, with a fair degree of certainty, the presence and extent of alveolar destruction in emphysema.

The relationship between pathology and function in the lung has long been a subject of interest. With regard to airway disease, there appears to be a good correlation between the obstruction in peripheral airways and the observed lesions. Additional knowledge of the physiological consequences of specific components of the lesions, such as goblet cell metaplasia, inflammation, scarring, mucus plugs, etc., is needed to determine their respective contributions to the resulting disability. Although alveolar destruction is associated with loss of recoil, it is not known whether the mechanical abnormality precedes the breakdown of alveoli. The stress-strain characteristics of lung tissue are important in this regard, particularly the measurement of yield-stress. An aspect of structure-function interrelationships which was virtually ignored until very recently, but is currently receiving considerable interest, is the study of the distribution of stresses through lungs, and the parenchymal distortions that result from unequal stresses. Such studies are absolutely fundamental in order to determine the role, if any, that the mechanical stress plays in the breakdown of alveolar walls.

The pathological abnormalities of established emphysema are well-described, although the earliest lesions are poorly understood. Those of chronic bronchitis are less well-described, although mucus gland hyperplasia and goblet cell metaplasia appear to be the characteristic abnormalities.

Further pathological studies, both descriptive and quantitative, are needed to identify the base of obstruction to airflow in peripheral airways, where early physiologic abnormality can now be detected.



The general pathology of the lung, and how it can react to injury, is not well-documented, although this knowledge is critical to the understanding of all lung diseases. With regard to emphysema, knowledge is needed as to whether alveolar wall breakdown is a nonspecific response to a variety of insults and derangements. Tissue destruction by proteolytic enzymes in experimental animals is well-documented, as is its occurrence in individuals with α_1 -antitrypsin deficiency. Emphysema has also been stated to result from a variety of other toxic agents although the resulting pathological abnormalities are less well documented.

Intercellular junctions are important determinants of cell function. The mechanism by which they act is only beginning to be unravelled. It is known that there are tight junctions both in the tracheobronchial mucosa and between type 1 alveolar cells. Whether or not abnormalities in these junctions are important in the pathogenesis of lung disease is unknown. However, it would seem that, in an organ continually exposed to inhaled particulates which are thought to be important in pathogenesis, the junctions must have a role in protecting the lung from injury.

More information is needed in the area of cell turnover rates in the lung. The rate of turnover of type 1 and type 2 cells, and for that matter of bronchiolar cells, remains an open question, although it is quite conceivable that emphysema could result from a decreased rate of replacement of type 1 cells. If a valid method of measuring turnover rates was acceptable, the influence of physiological, pharmacological, and environmental influences on this would provide invaluable information.



Pulmonary Defense Mechanisms

Research recommendations relative to these important functions of the lung are discussed extensively in Problem Area 7, Infectious Respiratory Diseases. They are applicable to all lung disease.

If chronic bronchitis is a nonspecific response to inhaled irritants, the defense mechanisms of the airways are obviously highly relevant. Most studies on the deposition of particles have been theoretical, and there is a need to validate these models experimentally. The influence of physiological, pharmacological, and pathological factors on deposition sites are virtually unstudied. There is considerable need for improved technology in this area as well as for studies of interactions between clearance rates and physiological variables and pharmacologic agents of the capacity of the tracheobronchial epithelium for regeneration, and of the viscoelastic and biochemical properties of mucus.

Particle clearance is closely associated with the problem of particle deposition. Although advances in isotope techniques have permitted studies in man, the methods are time consuming and difficult to standardize. While these techniques allow analysis of clearance of the whole tracheobronchial tree, virtually nothing is known about clearance rates from specific airways. Further work is needed with special reference to the effects of respiratory infections, smoking and other pulmonary insults.



Phagocytic cells also play an important role in pulmonary defense and the alveolar macrophage has been the subject of intensive investigation. In relation to the pathogenesis of emphysema, additional knowledge is needed about the ultrastructural and biochemical alterations in alveolar macrophages following exposure to physical, chemical and infectious agents. Questions to be answered are: Does release of proteolytic enzymes during phagocytosis play a role in the pathogenesis of emphysema? Do alterations in the metabolic functions of macrophages result in failure of their protective function, resulting in a predisposition to alveolar wall breakdown by environmental agents? What role do surfactant and secretory immunoglobulins play in inactivation and detoxification? What are the factors which normally keep the tracheobronchial tree sterile, and how does their failure result in chronic colonization of the tracheobronchial mucosa with bacteria?

2.3.4 Recommendations

In order to gain significant knowledge and understanding concerning chronic bronchitis and emphysema and in order to lead to reduction of incidence, morbidity and mortality, a number of areas must be further explored. The pathogenesis of chronic bronchitis and emphysema needs elucidation. Animal models and human studies are needed to evaluate the role in pathogenesis of the following: mucus secretion; defense mechanisms; relationship of pathology to function; cell turnover kinetics; surfactant control; distribution of intrapulmonary stresses due to parenchymal distortions; and intercellular junctions.

Studies are needed to: identify and characterize the chemical reactivity of proteolytic substances having access to the lung from serum, leukocytes, alveolar macrophages, platelets, and cathepsins of tissue origin; further characterize the structure, chemical reactions, and turnover of the serum inhibitors of proteolysis; explore the effects of deficiencies of alpha₁-globulin in animal models by means of depletion of alpha₁-globulin inhibition by specific alpha₁-antiserum; explore the chemical and physiological effects of proteolytic enzymes administered experimentally to overcome existing circulating or lung tissue inhibition.

Etiologic and risk factors should be identified through prospective, epidemiologic studies. The effects of infectious agents, community air pollution, role of smoking, genetic factors, and geophysical factors (climate, geography), should be evaluated. Longitudinal studies from childhood will identify risk factors and predisposition to chronic bronchitis and emphysema.

Further attention should be paid to the development of mechanical, electrical, and mathematical models of the lung in understanding the pathophysiology of chronic bronchitis and emphysema.

Early detection and diagnosis is of key importance in dealing with chronic bronchitis and emphysema. Standardization of definitions of these two processes and their overlapping presentation is essential to reproducible significant results in epidemiologic and other studies. Development of biochemical, immunologic, and physiologic abnormalities secondary to early chronic bronchitis and emphysema



should be identified. The newer, more sensitive tests of pulmonary function should be thoroughly tested in field trials.

Bioengineering has much to contribute to the research and development of early detection devices as well as to the development of new, more efficacious ventilatory assist devices. Such collaboration should definitely be encouraged.

Longitudinal, controlled evaluations should be performed to measure the extent of reversibility in patients who have been treated, quit smoking, or moved from an area of significant community air pollution. New criteria for identifying reversibility besides traditional pulmonary functions parameters might include mucosal biopsies, mucus clearance rates or other innovative parameters evolving out of the above described recommendations.

Current treatment modalities should also be evaluated. These include filter systems for removal of air irritants, humidity control devices, various pharmacologic agents, including those meant to decrease mucus viscosity, bronchodilators and antibiotics, presently used and newly developed mechanical devices, physical therapy, exercise training programs, psychological support, and prolonged oxygen therapy.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.



2.3.5 Summary

Emphysema and chronic bronchitis have been steadily, and now rapidly, growing as leading causes of morbidity and mortality in our society. In large part, this is due to cigarette smoking and most probably due to our increasing community air pollution burden.

The incidence of obstructive lung disease and emphysema in individuals who have the genotype associated with severely deficient α_1 -antitrypsin may be as high as 60 percent below age 60. Finally, the synergistic or additive role played by environmental factors in producing obstructive lung disease in α_1 -antitrypsin-deficient individuals might be very significant. Investigation into genetic mechanisms and the pathophysiology of protease inhibitor deficiencies is of importance.

The socioeconomic burden is tremendous with 1967 estimates of approximately \$1.2 billion. Significant research is needed in order to determine pathophysiology, etiology, and risk factors. Early diagnosis is possible through improved devices of early detection of biochemical, immunologic, or physiologic abnormalities. Current treatment modalities must be evaluated for efficacy, and future treatment devices and modes should be developed. One very important aspect for alleviation of morbidity and mortality is the elimination of cigarette smoking and air pollution. This was discussed under Problem Area 2, Environmental Respiratory Diseases. However, not only has prevention thus far been unsatisfactory, but the future outlook is not very optimistic. Therefore, we can expect increasing rates of incidence, morbidity and mortality and we must exert significant effort not only



in prevention but in the detection and diagnosis, and treatment and management of chronic bronchitis and emphysema.

2.4.1 Introduction

Respiratory diseases in children can logically fit under numerous classifications, including environmental factors, infectious disease, interstitial disease, acute and chronic respiratory failure, hypersensitivity disease, pulmonary vascular disease, and asthma. Two of the most important respiratory diseases are cystic fibrosis and hyaline membrane disease. There remains another group of respiratory tract disorders that have a special age prevalence and are designated "Upper and Lower Respiratory Obstructive Diseases in Children." These disorders include croup, epiglottitis, and bronchiolitis. They are most common in the first years of life and remain significant causes of morbidity and modest contributors to mortality in infancy.

Infants and young children respond to numerous insults to the respiratory tract by manifesting airway obstruction. This is surely in part because of the smaller dimensions of the airway which may be more easily obstructed with a given insult. Since the resistance to airflow is related inversely to the fourth power of the radius of the tube, it follows that the thickening of bronchiolar wall in children will cause a greater increase in airway resistance than in the adult. Also, the specific infectious agents that affect children may be involved in the development of severe respiratory obstruction. Allergic states seem to contribute to lower respiratory obstructive disease in some instances.



2.4.2 Magnitude of Problem

One reason for concentrating on upper and lower respiratory obstructive diseases in children is due to the relatively sparse amount of data presently available. Epidemiologic studies will aid in defining these disease entities and their incidence during the first years of life, and will provide an estimate of morbidity and and mortality. Croup and bronchiolitis are commonly seen in pediatric practice, and epiglottitis more rarely. It is important to determine if these disease states are manifestations of a predisposition toward developing adult chronic obstructive lung disease, or, in fact, if these disease states contribute to the development of adult chronic obstructive lung disease.

2.4.3 Current State of Knowledge

Croup and epiglottitis are disorders of young children characterized by upper airway obstruction. The onset is typically sudden and occasionally leads to total airway obstruction with fatality. This obstruction may follow a seemingly minor upper respiratory infection but may occur without any antecedent infection. There have been viruses associated with croup but it occurs acutely and spasmodically and is more related to temperature changes or atmospheric disturbances than to infection. Epiglottitis, on the other hand, is most frequently associated with hemophilus influenza infection.

Lower airway obstructive disease, often called bronchiolitis, is most common between the ages of three and fifteen months. It is most unusual in the first month or two of

life and typical bronchiolitis is rare in older children. It would be most appropriate to consider bronchiolitis as a syndrome in which a specific etiology can be identified in only approximately two-thirds of the patients. The respiratory syncytial virus is presumably one of the more common of the viral agents that can cause lower airway obstructive disease but adenoviruses may do the same thing.

Respiratory syncytial virus (or other viral agents) can be identified in nasopharyngeal secretions by the immunofluorescent antibody technique in about two-thirds of the patients. In the remainder, no definite etiology is found. The clinical picture is characterized by overt respiratory distress and severe tachypnea. Cyanosis is not uncommonly present. The lungs become hyperinflated and this may usually be detected by chest X-rays.

Infants in the first months of life are known to be relatively immunologically deficient since the antibodies passively transferred across the placenta from the mother are present in only small amounts after several months, and the infant's own ability to make antibodies is not well developed. Although the role of altered immunological responsiveness has been mentioned in the pathogenesis of bronchiolitis, few studies have documented the nature of the altered host response. Little work, for example, has been done with lymphocyte-associated, cell-mediated immunity.

The role of adenoids in resistance to infection in the first years of life deserves much further study.



There is a paucity of information on optimal methods of management of either upper or lower airway obstructive diseases in children. There are advocates of cold mist or warm mist or dry air or oxygen without very careful evaluation of the effects of these modalities of therapy. Others have advocated bronchodilators and corticosteroids, but little data exist to support their use as therapeutic agents. The possibility that recurrent episodes of bronchiolitis in infancy may be the first attacks of asthma has been mentioned a number of times and deserves further evaluation. The long-term effects of lower airway obstructive disease in children are not unknown.

Very few individuals have addressed themselves to the study of airway obstruction in children. Not only are the morphologic characteristics of the young airway poorly documented, but the effects of alteration in size and distensibility on function are poorly understood. Relatively few studies have been devoted to the identification of factors leading to bronchiolitis or croup. The technology for evaluation of cardiopulmonary function in the first years of life has been lacking so that it has been very difficult to make objective measurements of airway function. Finally, a significant deterrent to advances in this area is the lack of an animal model. This is needed to evaluate various modalities of therapy apart from clinical trials. Clinical trials are complicated because of the variability in the disease and its course. Informed consent represents another problem.

2.4.4 Recommendations

A major approach is to define the many causes of lower airway obstructive disease in children and to sharpen the definition of the syndromes. This would require epidemiological approaches, long-term follow-up studies, measurement of physiological derangements, careful documentation of the etiology in each instance, including evaluation of the immune state, as well as critical evaluation of therapy.

Long-term prospective studies of children with respect to analysis of the possible role of air pollutants, allergic states, and intercurrent infection are in order, particularly with respect to designating the infant or child at risk of having chronic airway obstructive disease as an adult. Total eosinophile counts and IgE estimates should be studied.

Another major attack strategy is to study the normal lung at different ages. For example, the response of the lung to a given insult may be age-dependent and in some respects size-related. Neural and pharmacologic responses of relatively immature airways can also differ from those of the mature lung.

Another major attack would be a technological one to improve roentgenographic means of assessment of pulmonary function, as well as noninvasive methods of evaluation of cardiac and pulmonary function. Improvement in technology to measure airway conductance would be of great importance.



A final major approach should be a much more systematic evaluation of the various physical and chemical forms of therapy now in use. For example, the effects of temperature, humidity, and mist on the upper and lower airway resistance are long overdue. The evaluation of drugs that affect the autonomic nervous system, as well as other forms of bronchodilators and expectorants by carefully controlled clinical trials, would be important.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.

2.4.5 Summary

Upper and lower respiratory obstructive diseases in children are in need of further definition and investigation. Airways in developing children need to be better understood specially in light of their contribution to adult chronic obstructive lung disease. Croup, bronchiolitis, and epiglottitis should be investigated as to efficacious modes of therapy, early detection, and prevention. Obstructive lung diseases in children could be a manifestation of their predisposition toward developing adult chronic obstructive lung diseases, or in fact, might contribute to that development.



2.5 ALLERGIC AIRWAY DISEASE--ASTHMA

2.5.1 Introduction

This Problem Area includes asthma or chronic reversible obstructive airway disease. It is defined as a disease characterized by an increased responsiveness of the trachea and bronchi to various stimuli, and is manifested by difficulty in breathing due to generalized narrowing of the airways. Individuals with a history of asthma usually show a raised sensitivity and increased reactivity to vasoactive amines. They react with bronchial constriction, mucosal edema, hypersecretion of mucus and abnormal cellular infiltrates. Predisposing factors include: a genetic predisposition in some families; a local end-organ hypersensitivity to pharmacologic agents, irritants and specific allergens; and a special form of immunologic response, leading to the release of specific chemical mediators. This Problem Area pertains to the neuropharmacological and immunological aspects of the control of airways and the derangements which occur in asthma.

2.5.2 Magnitude of Problem

Asthma is the most common chronic pulmonary disease. Because it can start in early childhood and can last a lifetime, it may result in a great deal of disability both in terms of education and employment productivity. The differentiation of asthma from chronic bronchitis and emphysema in some patients may be difficult. It should be remembered that even when emphysema is apparent, an additional component of bronchial asthma, which is treatable, may be present.



Although there are patients with coughing, wheezing and dyspnea due to a variety of cardiac and respiratory diseases such as cardiac asthma, mitral stenosis, chronic bronchitis, emphysema, pneumoconiosis, and obstruction of major airways due to neoplasm, these are logically excluded from the diagnosis of bronchial asthma and will not be discussed in this Problem Area.

Although the annual mortality rate is relatively small (2,500 per year), asthma is a remarkably common illness. Several surveys indicate that about 4 percent of persons in this country, i.e., about 8.6 million, have active asthma. It is a frequent cause of disability, being responsible for 5 percent of all chronic disabilities. In one year, it accounted for 85 million days of restricted activity, 33 million days in bed, and 5 million days lost from work. Among children, asthma causes the loss of 6.48 million school days; among chronic diseases, asthma is the number one cause of loss of time from school. It also causes an annual loss of 7 million work days, an average of 7.4 work days per affected employed person. From a personal viewpoint, it is a particularly uncomfortable illness, and because of its chronic nature and variable course, it may last years, even a lifetime.

Asthma is a large burden on the health care system. In 1968 there were 135,000 patients discharged from hospitals with a diagnosis of asthma or hay fever, with an average hospital stay of 8.3 days. In a recent year, 27 million patients' visits were made to physicians because of asthma.



2.5.3 Current State of Knowledge

At the present time, it is not possible to be definitive regarding the genetic basis of asthma even though the literature on the subject is quite extensive. This state of affairs will probably continue until physicians can unambiguously define asthma. The heterogeneity of the disease probably derives from both genetic and nongenetic causes, and makes the natural history of asthma difficult to characterize. Studies of familial incidence of asthma conducted in the last century indicate the probability of multifactorial inheritance patterns. The mechanism by which certain agents result in sensitization of atopic individuals and why these agents apparently sensitize one atopic person rather than another are not understood.

Longitudinal studies are needed to learn the genetic, pharmacological and immunological abnormalities in different populations of asthmatics.

Patterns of incidence of asthma are to a great extent determined by the allergens in the environment. Recognition of allergens in the environment, such as the house dust mite, a variety of molds, castor bean antigen, etc., is essential to be able to avoid or diminish exposure to such agents.

The role of infection in asthma has not been clarified. It is not known at this time whether such a condition as bacterial allergy exists in patients with bronchial asthma. Nevertheless, it has recently been shown that bacterial products such as enzymes from *Bacillus subtilis* are potent sensitizing agents. Further detailed bacteriological and virological

studies are needed to determine which bacteria and viruses are associated with asthmatic attacks. Children with more than one bout of bronchiolitis and a positive family history of allergy are at greater risk for developing asthma.

In people with the appropriate immunologic constitution, exposure to a variety of environmental antigens, both natural and artificial, leads to the production of a unique kind of immunoglobulin, IgE. Although this protein is found in small amounts in nonallergic people, it is present in larger amounts in patients with allergic asthma. It represents antibodies to the environmental antigens and has the capacity to attach to certain cells (tissue mast cells or basophils in the mucous membranes and skin. According to the mast cell theory of asthma, airborne antigen comes in contact with IgE cell-bound antibody at the surface of these cells. The antigen-antibody reaction causes the mast cell to release mediators, such as histamine and the slow-reacting substance of anaphylaxis (SRS-A), which travel short distances to act on smooth muscle, secretory mucous glands and blood vessels to produce bronchospasm, hypersecretion of mucus and edema. Chemotactic factors, which cause wandering inflammatory cells to accumulate, are also released.

However, the specific stereochemical requirements for antigens and IgE interaction on the cell surface leading to the mediator release are not known. The sites of antigen disposition in airways in the reaction of antigens with host defenses, and how antigens are degraded and eliminated, are poorly understood. There is only very limited knowledge on the role of cellular mechanisms in asthma.



The mechanism of hypersensitivity to agents such as histamine and methacholine is unknown. One theory is blockage of beta-adrenergic receptors in the lung and perhaps elsewhere. Another theory is that the induced changes in the ordinary control mechanisms and exaggeration of vagal reflex responses is responsible. The interrelations between the adrenergic and cholinergic systems in allergic-induced or irritant-induced bronchospasm are not known. More must be learned about the neuroreceptors and the neurotransmitter mechanisms within the central nervous system and airway control.

The chemical and physical nature of mucus and the control of its secretion in man are poorly understood. The pulmonary defense mechanisms such as the mucociliary transport of the asthmatic lung have received little attention. Recent technological advancements and newly available radioactive isotopes have accelerated and broadened experimental investigation of particle disposition and retention in the human respiratory system.

Studies are needed to determine the pulmonary function abnormality and the site of airway obstruction in asthma. Better methods for measuring changes in airway caliber and resistance are being developed. Closing volume techniques appear promising in disclosing early changes in small airways.

Human model systems have obvious advantages and disadvantages. On a cellular level, means of isolating relevant cells (e.g., basophils and mast cells) from blood and tissues should be improved. On an organ level, the use of normal human lung passively sensitized in vitro has been helpful. An obvious obstacle is obtaining lung tissue from asthmatic

individuals without necessitating surgical intervention. Perhaps cell culture lines can be used, depending upon how well the differentiated properties of such cells remain.

There is a need for improved models of asthma in animals. An animal model exists in which hypersensitivity to histamine can be induced in certain strains of mice by pertussis vaccine or beta-adrenergic blockage. But all animal models below primates have the obvious disadvantage that their immunological systems, with regard to cytophilic antibodies like IgE, may be different from humans in important ways. Primate models have the important advantage that human IgE can be passively transferred to them. Several laboratories are investigating mediators and mediator release in passively sensitized primate lung tissue.

In addition, the control mechanisms of immunological and nonimmunological mediator release from basophils and mast cells is being investigated. The role of cyclic AMP and of adrenergic and cholinergic mechanisms pertaining to the release of mediators, as well as the role of the lymphocytes in asthmatics and their response to the stimulation of adenylcyclase, are also being investigated.

2.5.4 Recommendations

The tendency of asthma to occur in families underlines the importance of an understanding of the genetic factors involved in the etiology and pathogenesis of this disease. Studies are needed to identify the immunologic reaction patterns of persons who develop asthma. The role of IgE in the normal host defense mechanism needs to be determined.

The mechanism of why increased levels of total and specific IgE occurs in atopic asthmatics also needs to be studied. The sites of antigen deposition, and how they are degraded and eliminated needs to be understood.

Mechanisms involved in control of airways are both complex and poorly understood and elucidation of these mechanisms is essential to effective therapy as well as prevention of asthma. A major strategy should be to determine the mechanism of bronchial hypersensitivity of asthmatics to histamine, methacholine and other mediators. Studies should be directed to determine if there are genetic defects in cyclic AMP metabolism or mediators synthesis or release. Neural pathways and reflexes controlling airway resistance need to be worked out in the normal and the asthmatic, as well as their relation to release of mediators, and the biochemical targets of these mediators must be identified. This research could progress considerably if an animal model were available, thus permitting studies that would be inappropriate in patients. Primate models are needed for the study of etiology and pathogenesis of asthma.

The natural history of asthma is ill-defined. Longitudinal studies are needed to follow genetic, immunologic, pharmacologic and physiopathologic characteristics in different populations of asthmatics.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.



2.5.5 Summary

Allergic airway disease represented by asthma constitutes a very significant national health problem. Approximately 4 percent of Americans have active asthma and the annual mortality is approximately 2,500 per year. Asthma is responsible for 5 percent of chronic disabilities and in one year accounted for 85 million days of restricted activity. In 1968, it was estimated that 134,000 patients were hospitalized for asthma or hay fever with an estimated cost of approximately \$125 million. Investigation needs to be conducted in man and animal models focusing on the pathophysiology of asthma, especially concerning IgE dynamics and responsitivity of bronchial airways and vascular bed. Programs to evaluate present diagnostic and therapeutic techniques should be instituted, and investigation into the development of new and innovative modes of diagnosis and treatment should begin.



2.6.1 Introduction

This Problem Area is addressed to idiopathic chronic diffuse interstitial pneumonitis; collagen diseases (more appropriately designated "acquired connective tissue diseases"); and diffuse pneumonitis resulting from drug reactions and radiation fibrosis.

Because they are covered under other Problem Areas, the following diseases are not included: noninfectious granulomatosis (including sarcoidosis); occupationally induced interstitial fibrosis; hypersensitivity pneumonitis; and acute respiratory failure.

Except for the diffuse pneumonitis that results from radiation or drug reactions, all diseases discussed below are of unknown cause but have in common a number of clinical, physiological and pathological features. The one most consistent finding is significant reduction of pulmonary diffusing capacity, often to very low values. Whether there is a defect in gas transfer through a thickened membrane, reduction in available surface area, or ventilation-perfusion inequality is controversial. In the views of some, reduction of diffusing capacity during exercise remains the best indicator of diffuse interstitial diseases.

Roentgenographic evidence may be minimal or unrecognized early in the disease process. In more advanced disease, the characteristic abnormality is diffuse nodular densities and linear fibrosis, most marked at the bases, and lung volume decreases as fibrosis progresses.



Lung biopsy findings, observed by usual light microscopy, vary from very early interstitial edema with lymphocytic infiltration to extensive severe fibrotic distortion (commonly termed "honeycomb lung"). These changes serve as an essential starting point to exclude sarcoidosis, silicosis, asbestosis and have been useful in classifying the various types of idiopathic interstitial fibrosis. Although there is some controversy over the separation of the "usual" and the desquamative interstitial pneumonia, desquamative interstitial pneumonia usually responds quite well to prednisone while the benefits in usual interstitial pneumonia have been disappointing.

Acquired connective tissue diseases usually involve the bronchi and lungs, although the frequency of involvement varies widely. In rheumatoid arthritis, pulmonary changes include pleurisy with or without effusion, multiple pulmonary nodules, rheumatoid pneumoconiosis or Caplan's syndrome, progressive interstitial fibrosis and pulmonary arteritis with pulmonary hypertension. The prevalence of diffuse interstitial pulmonary fibrosis varies widely in reported series. In patients with high rheumatoid factor titers, pulmonary involvement has been as high as 23 percent, but in the majority of reports it is difficult to be sure of the actual type of pulmonary involvement.

As the differential diagnosis between the rheumatoid lung and the usual interstitial pulmonary fibrosis is frequently impossible from the lung biopsy alone, immunofluorescent studies to demonstrate large amounts of gamma M rheumatoid factor in the alveolar walls and pulmonary capillaries may be helpful. However, a high incidence of positive rheumatoid



factor in patients with diffuse interstitial fibrosis without any evidence of rheumatoid arthritis has been well-documented.

In systemic lupus erythematosus (SLE), the second most common connective tissue disease, pleural effusion is the most frequent form of pulmonary involvement, occurring in about one-half of patients. Immunosuppressive drugs have been reported to be useful in SLE, and the diffuse interstitial lung lesion has been reported to have improved with treatment. There is a growing body of evidence that immunologic reactions are involved in the pleural inflammation and pulmonary vascular reactions of systemic lupus, and there is reason to believe that they may also be involved in rheumatoid lung.

In progressive systemic sclerosis (scleroderma), the lung is involved in almost all patients. Pulmonary function abnormality frequently precedes any roentgenographic evidence of the disease, and death from pulmonary scleroderma is common, ranking in frequency after cardiac and renal causes.

Pulmonary changes in reactions to drugs are similar to, if not indistinguishable from, the type of tissue injury in the lung in idiopathic interstitial pneumonitis. In radiation pneumonitis, the acute phase occurs 3 to 6 weeks after cessation of radiation therapy. Hodgkin's disease treated with upper mantle therapy provides an excellent model to study patients without significant pulmonary parenchymal abnormality and in whom baseline pulmonary function tests can be obtained. Of particular interest in these patients is



associated derangement of cell-mediated immune response, which may be used as a model for immunological study in relation to the development of fibrotic response to radiation therapy.

It is noteworthy that the lung tissue responses leading to pulmonary fibrosis are similar to lung responses to injury from radiation or noxious agents.

2.6.2 Magnitude of Problem

The incidence of the usual diffuse interstitial pneumonitis is not known as the disease is neither well-recognized nor classified. However, it appears not to be a rare disease and in many areas of the country it exceeds the incidence of sarcoidosis and hypersensitivity pneumonitis. From a report of nontuberculous referrals, 951 (20 percent) of 4,751 referrals from 1949 to 1971 had interstitial disease. Of the 951 cases of interstitial disease, 277 were classified as due to occupational or environmental factors. A reasonable estimate would be that 10 to 15 percent of the referrals to a pulmonary unit suffer from the usual diffuse interstitial pneumonia. In 1967, there were 1,614 deaths from respiratory disorders from collagen disease and 4,218 from diffuse fibrosis. Among acquired connective tissue diseases, rheumatoid arthritis occurs in about 500 per million population per year, SLE in about 30, and progressive systemic sclerosis in about 12. SLE is about twice as common in blacks and in females.



2.6.3 Current State of Knowledge

Natural History

Little is known about the natural history of the pulmonary component of these diseases. No reliable information is available as to whether the usual interstitial pneumonitis in rheumatoid arthritis and lupus is slowly progressive, or whether there are periods of stability followed by periods of recurrent lung damage. Clinical studies should emphasize the natural history of these diseases. Early recognition is essential to studies of their natural history. Patients suspected of showing radiographic changes should be studied clinically, including appropriate assessments of pulmonary function. If pulmonary function is sufficiently abnormal, lung biopsy should be considered.

Early recognition is impeded because the very fine and diffuse nature of the early interstitial change makes the early roentgenographic recognition of these changes difficult, and pulmonary function tests in most hospitals are only the simplest ventilatory studies; hence, they are unlikely to provide evidence of early diffuse interstitial change. The most promising approach to early diagnosis is to study patients accepted as being at highest risk, i.e., those with any of the acquired connective tissue diseases, especially rheumatoid arthritis, systemic lupus erythematosus and progressive systemic sclerosis.

Elucidation of the natural history is also important to the development of appropriate therapy. In longitudinal studies the worsening patient can be identified and considered for controlled therapeutic studies with promising regimens.



Etiology

Immune injury is believed to play a central role in the usual interstitial pneumonia, but genetic factors seem to modify susceptibility to, and expression of, the disease. Exogenous agents, including viral infections, some drugs, and radiation are also implicated as etiologic factors.

Immunologic responses have become of increasing interest. A high percentage of patients with diffuse interstitial lung diseases have antinuclear as well as rheumatoid (gamma globulin) factors. The majority of patients have increased immunoglobulins in a pattern similar to that in autoimmune diseases. It has been suggested that T-lymphocytes (thymus-derived cells) play a vital role in preventing autoimmunity through two mechanisms. T-lymphocytes are normally unresponsive to autoantigens, but they cooperate in immune responses with B-lymphocytes (not thymus-derived cells), which are precursors or antibody synthesizing cells in many situations. Also, virus infections may cause T-lymphocyte sensitization, and this could stimulate B-lymphocytes to produce "autoantibody." Possible clinical examples are the presence of antinuclear antibodies in some cases of idiopathic pulmonary fibrosis with a history of preceding virus-like respiratory infection and in patients treated with drugs (such as hydralazine) that may produce an interstitial pneumonitis.

Genetic predisposition to various connective tissue diseases, especially systemic lupus erythematosus, is suggested by the tendency for it to occur in monozygotic twins and in families. Similarly, it has been established that relatives of patients with usual interstitial pneumonia have a high risk of

developing this disease. Families of patients with interstitial pneumonitis should be carefully evaluated. Moreover, the fact that not all patients with Hodgkin's disease who receive irradiation develop post-radiation fibrosis is evidence of host factor differences. The challenging question is what factors are operative in influencing the development of a fibrotic reaction in about one-half of the patients while others with the same irradiation dose escape.

Some of the genetic factors influencing the development of pulmonary fibrosis may be elucidated through studies of HL-A (transplantation antigens) histocompatibility groupings in interstitial pneumonias, including those associated with acquired connective tissue diseases. Studies in patients who develop a diffuse pulmonary lesion secondary to various drugs such as hydralazine, hexamethonium, busulfan, and nitrofurantion may furnish additional information as to the type of immunological injury that is produced as well as an opportunity to evaluate host variants.

Viral infections are of interest as etiologic agents that might alter the antigenic configuration of host cells so that they become the target of autoimmune assault. Preliminary investigations suggest that viral agents may be associated with systemic lupus erythematosus.

Pathogenesis

Elucidation of factors affecting collagen metabolism, especially its syntheses and degradation, could lead to understanding the development and course of pulmonary fibrosis and in turn to specific intervention to prevent fibrosis.



At some point in time, knowledge of collagen metabolism will approach a level where this ultimate aim will be attainable through either decreasing the synthesis of collagen, interfering with maturation of collagen, or by stimulating collagen degradation. However, from a biochemical and metabolic point of view, regulating collagen metabolism in the lung is a difficult task because of the slow turnover rate compared to that of collagen in other organs. Because of the diseased state, collagen synthesis in the lung is enhanced and a differential turnover rate of collagen in normal and affected tissue may favor the therapeutic effect on newly synthesized collagen. The unique structure of the lung with its communications with outer atmosphere could allow administration of therapeutic agents in the form of an aerosol permitting a higher deposition of the drug in the lung.

In addition to factors controlling some specific steps of collagen metabolism, several other factors having nonspecific effects on the reactivity of connective tissue play an enormous role in the development of fibrotic lesions. Most discussed, but still poorly understood, are the genetic factors. The enormous inter-individual variability in connective tissue reactivity could be explained by the existence of various constitutional "mesenchymal" reactivity types, as suggested by several investigators. To prove this is a difficult but important task. To understand the meaning of individual reactivity reflected in great variations in the magnitude and dynamics of lung injuries, studies should be addressed to neurogenic, hormonal and enzymatic mechanical and nutritional factors.



Models

A good animal model for diffuse interstitial lung disease has been difficult to develop. Airway administration of various materials has produced interstitial lung damage, but this damage has not evolved into a condition which closely resembles human disease.

Essential anatomic criteria for an animal model include: a mixed cellular exudate in the interstitium; protein exudate in air space, with or without leucocytes; proliferation of lining epithelium; gradual progression to fibrosis and honeycombing; continuing activity, even when partly fibrotic; and diffuse distribution with possibility of normal zones interspersed with diseased areas.

A pulmonary lesion in Syrian golden hamsters caused by subcutaneously administered N-nitrosi-N-methylurethane has been noted to resemble fibrosing alveolitis in man. In an extension of these studies, lesions were produced by weekly subcutaneous injection of varying doses of the drug and were stopped at various times. Development of the lesion resembled that of the usual interstitial pneumonia or fibrosing alveolitis. Repair of this damage appeared to involve the proliferation of type II epithelial cells. Later, the alveoli became lined by bronchiolar epithelium. Although there is species variation, the same type of lesions are now being developed in the dog. This model should be explored in several species of animals, including primates. Such a model would lend itself to serial physiological studies as well as to obtaining material for investigating immunological changes concurrent with, or secondary to, this type of pulmonary lesion.



Diagnosis

Long biopsy material should be obtained on as many early lesions as feasible. Biopsy material should be cultured for fungi, tubercle bacilli, and especially for virus. Ultra-structure studies for changes compatible with virus infections would be of special importance.

The serum levels of various immunoglobulins, rheumatoid factor, antinuclear factors, and anti-DNA are useful. There is evidence that rheumatoid arthritis and systemic lupus erythematosus occur more frequently in patients with low IgA. All of these studies are helpful in an attempt to separate SLE and possible rheumatoid disease from the usual interstitial lung diseases.

2.6.4 Recommendations

Prevention

Most studies today have been addressed to the physiology of the lung; and it would appear that more investigation must be directed to the cellular function and how these are altered by immunologic competence and genetic factors. Since it is difficult to study biochemical and other submicroscopic functions of the human lung, it is important that animal models be developed to explore the following problems/projects in some detail: the relationship of structure and function, the study of the relationship of biochemical function and alterations in metabolism (phospholipids, protein, collagen, glycoproteins, etc.) to the pathologic and physiologic changes; the determination of the physiologic changes in various entities and the relationship of these to the above mentioned



studies; the identification of genetic variations in lung structure and function as they relate to development of interstitial diseases; the study of the deviation from normal defense mechanism in the disease entities such as collagen vascular diseases and in animal models; and the determination of response to injury in animal models and longitudinal follow-up to determine evolution of pathologic changes.

Although the physiologic abnormalities associated with interstitial lung diseases are well known, as are the pathologic changes, little is currently understood regarding the precise etiologic factors. The lung appears to respond in a similar way to a number of disease entities (as determined by light microscopy). There is a great need for animal models to be developed where exposures could be performed using elements that are suggested from epidemiologic studies of human disease; studies should include careful epidemiologic evaluation to determine host factors; environmental factors, and other related elements that might be common to a group or single interstitial disease. A group of interstitial diseases such as collagen diseases might serve as a prototype. The work should study genetic variations in response to lung injury by various agents and attempt to characterize, both immunologically and with respect to compatibility, patients who suffer from interstitial diseases.

It should examine the role of viral agents in these diseases. It would also seem appropriate to take careful drug histories on all patients who develop these diseases since there are currently available animal models of interstitial lung diseases produced by a number of drugs mentioned in the



introduction such as hydralazine hydrochloride, busulfan and hexamethonium. Since radiation is known to produce interstitial diseases, it could provide a good animal model and, in addition, will enable the trace of the development of disease in patients with Hodgkin's disease who receive extensive radiation. It is hoped that in the epidemiologic studies it will be possible to also identify environmental factors which may be common to people developing the disease, since it is known that inhaled substances can produce interstitial disease (berylliosis).

While risk factors in most interstitial diseases have not been identified, a few have been, and it is of interest to determine how to control these risk factors. Studies should be directed at the effects of diminished environmental factors accomplished by filtering air, use of masks, etc. Studies on the effect of modifying the nonpulmonary manifestations of diseases such as collagen diseases should be made with respect to lung function. A vigorous attempt should be made to identify the risk factors including genetic, allergic, and other altered immune responses.

Detection and Diagnosis

Efforts must be made to improve the sensitivity of currently available diagnostic tests, such as the chest X-ray, for early detection of disease. Efforts should be made to improve the diagnostic effectiveness of the chest X-ray, utilizing, for example, computer analysis of densitometry readings and exposure variation and the calculation of dose and exposure factors.



Biopsy material is currently the only way to establish the diagnosis of interstitial lung diseases, and work should be continued on improving needle biopsy techniques. Open lung biopsies offer the possibility of obtaining fairly large specimens of tissue on which extensive investigation can be performed along the lines mentioned earlier.

Patients' immunologic competence should be studied in detail and should be matched with studies of the biopsy material regarding cell-mediated immunity, autoantigens, competence of the lymphocytes, and localization of immunoproteins in pathologic specimens.

Treatment and Management

Except for steroids and antimetabolite drugs, there is little therapy currently available for the interstitial respiratory diseases. It is important, then, to evaluate the role of corticosteroids through studies in humans and animal models and also to evaluate immunosuppressive therapy in a carefully controlled randomized prospective study. Although physiologic measurements have been used to gauge the effectiveness of the therapy, examination of a cellular characteristic, immunologic competence, and biochemistry of expectorated alveolar cells may merit investigation.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.



2.6.5 Summary

Diffuse Interstitial Respiratory Diseases considered in this Problem Area include idiopathic chronic diffuse interstitial pneumonitis; collagen diseases, more appropriately designated "acquired connective tissue diseases;" and diffuse pneumonitis resulting from drug reactions and radiation fibrosis. With the exception of diffuse pneumonitis resulting from radiation or drug reactions, the rest of the diseases are of unknown etiology.

Usual diffuse interstitial pneumonitis is not a rare disease and in many areas of the country it exceeds the incidence of sarcoidosis and hypersensitivity pneumonitis. In 1967, there were approximately 1,614 reported deaths from respiratory disorders secondary to collagen disease, and 4,218 from diffuse fibrosis. The incidence of some of the collagen diseases, such as systemic lupus erythematosus, is four times more common in blacks than whites.

Research is required to determine the etiology and pathogenesis of these disorders. This work is predominantly needed at the cellular function level rather than at the organ level. Prospective epidemiological studies will be necessary to shed light on natural history, incidence, etiology and risk factors.

Early detection and diagnosis should focus on improved means of radiographic analysis, possibly utilizing densitometry and automated scanning. Also, research into characterizing cellular dysfunction might lead to early diagnosis by analyzing alveolar macrophages. This technique would be



noninvasive. Finally, more simple, efficacious, and safe biopsy techniques should be developed.

Present treatment and management is limited, and controlled studies of the efficacy of corticosteroids are needed. Also, research into new pharmacologic agents which might retard the development of fibrosis should be conducted, initially utilizing in vitro and animal studies.



2.7 INFECTIOUS RESPIRATORY DISEASES

2.7.1 Introduction

This Problem Area addresses itself to identifiable infectious diseases of the tracheo-bronchial tree that occur either as self-limited episodes or as chronic diseases leading to lung destruction.

2.7.2 Magnitude of Problem

Infectious pneumonitis, one of the most frequent health problems in this country, is the single most common cause of hospitalization due to respiratory disease. Infectious pneumonitis from all causes was responsible for about 2.7 million hospitalizations in 1970, or 8.5 percent of the 33 million hospital discharges surveyed in that year. In addition, it accounts for about 1 percent of nosocomial (hospital-acquired) infections, which have been estimated to delay discharge from the hospital by approximately 7 days. Thus, estimating 329,000 patients who develop infectious pneumonitis while hospitalized, more than 2.3 million hospital-days are added to those for the basic illness.

In 1968, infectious pneumonitis caused approximately 66,000 deaths in this country. For children less than one year old, approximately 12 percent of all deaths were due to respiratory diseases; infectious pneumonitis accounted for a majority of these. "Excess mortality," a term used to indicate deaths that occur beyond the number predicted for a given period of time, is frequently a consequence of respiratory infections. Between 1957 and 1972, influenza infections alone accounted for 275,000 "excess deaths."

On the basis of data available for 1967, the total cost of infectious pneumonitis has been estimated to be over \$2 billion. This is probably an underestimate.

2.7.3 Current State of Knowledge

Etiologic Factors

Organisms producing primary infection of the lung include bacteria, viruses, mycoplasma, mycobacteria, and fungi.

Approximately 80 percent of bacterial pneumonias are caused by *Diplococcus pneumoniae*. Incidence of pneumococcal disease is estimated at one case per thousand persons per year. In patients with bacteremic pneumonia the mortality rate varies with age from 9 percent in individuals less than 50 years of age, to 30 percent in those 50 years or older. It is estimated that 200,000 deaths per year could be prevented if an effective vaccine were administered to all older adults.

Despite the decline in *Bordetella pertussis* which followed the use of standardized pertussis vaccine, there remain a number of poorly defined but potentially important problems.

The level of protective immunity achieved by the administration of DPT vaccine in childhood lapses by the time an individual is in his teens. Adult type pertussis may be of more than nuisance concern. In view of the possible importance of childhood whooping cough in the genesis of adult pulmonary disease, it is reasonable to assume that adult type pertussis might also be significant.



Mycoplasma pneumonia develops in 3 to 10 percent of infected persons. Although infection is known to occur in epidemics among military populations and in household outbreaks, its epidemiology and true incidence remain to be elucidated. The role of antibiotic therapy in modifying the spread of infection is unknown, and circumstances analogous to the "immune carrier state" may exist.

Mycobacterium tuberculosis continues to be an important problem in the United States among low socioeconomic groups. The current approach toward tuberculosis control, by detection of infection (tuberculin testing) and chemoprophylaxis has encountered a series of recently recognized difficulties.

Major causes of nosocomial pneumonia are gram negative bacilli, staphylococci and other opportunistic agents, which colonize seriously ill patients and create serious problems that require better understanding of host defense mechanisms and careful epidemiological studies.

Pneumocystis carinii infections are being recognized with increasing frequency in patients receiving immunosuppressive agents and steroids after organ transplantation. There is need for rapid noninvasive diagnostic procedures to identify such infections as a step to early therapy.

Environmental toxic agents are associated etiologic factors. For example, there is a well-defined relationship between silicosis and susceptibility to tuberculosis. The influence of low socioeconomic position (crowded quarters, poor heating or cooling, accumulation of garbage and resultant pests, etc.) requires further study as a complex cofactor influencing infectious diseases.



Host Defense Mechanisms

Host defenses have a major role in preventing the establishment of infections, or in limiting the multiplication and spread of microorganisms that cause infectious pneumonitis.

Transport pathways and mechanisms for processing particles which reach the lung contribute to host defenses. Mucous transport in the bronchi depends upon the integrity of ciliated epithelial cells and on the quantity and constituents of mucus. It has been demonstrated that many toxic agents interfere with ciliary action and also stimulate secretion of mucus. Destruction or alteration of this transport system delays clearance of deposited material and increases storage in the lung, which may lead to increased susceptibility to bacterial infections. Studies are needed to test this hypothesis.

Methods are available to collect sufficient quantities of tracheal mucus via tracheal pouches, esophageal cannulae, etc., to characterize the properties of mucus in healthy animals and those with induced disease, and to compare with data on animal cervical mucus. Studies should be extended in vitro to evaluate changes in permeability, hydration, ion concentration and pH on defense functions.

The generation and flow of lymph from the distal alveolar ducts, the precise role of lymphatic pathways in normal clearance, and their role in augmenting transport during inflammation are unknown and their involvement in different diseases should be investigated. These primary and secondary transport pathways are particularly important in

infectious pneumonitis, since the establishment of inflammation in the lung leads to the recruitment of additional transport pathways to deal with multiplication and spread of infectious agents.

The alveolar macrophage system, another important component of host defense systems, depends primarily upon the metabolic and enzymatic apparatus of the alveolar macrophages. Their many intracellular factors, which function to contain or eradicate microorganisms include the lysosomal enzymes and the microbicidal substances (such as hydrogen peroxide), which are elaborated in the metabolic burst accompanying the phagocytic process. The alveolar macrophages can be augmented by the recruitable phagocytic systems of bone marrow.

Particle uptake is influenced by the presence of opsonins, specific antibodies, cellular immune factors, etc., which in turn, depend upon local and systemic production of the several classes of immunoglobulins plus immune lymphocytes. The potential for defective function in the uptake and intracellular processing of particles during phagocytosis are multiple. This complex of mechanisms, that ends with phagocytosis as a final common pathway, has received a great deal of study in vitro, but relatively little in the lung. Studies of alveolar macrophages have been based largely on cells obtained by washout techniques and relatively few studies have been performed on the phagocytic system in vivo. Since in vivo and in vitro phagocytic conditions vary considerably, efforts should be directed at developing methods for in vivo measurement of phagocytosis for comparison with the studies on lung washout cells.



Surfactant--which has been extensively studied as a physical layer on alveolar cells that promotes alveolar stability should be investigated as an alveolar defense mechanism. It should be studied in vitro for its effects on bacteria and viruses in relation to phagocytosis of these cells, and in vivo to determine whether specific metabolic alterations modify its defense capacity.

Pathogenesis

Infectious pneumonitis occurs because of breakdown of a complex of systems involving tissue architecture, transport mechanisms, phagocytic mechanisms, antibodies, cellular immunofactors, and metabolic responses. Endogenous disease or environmental toxic agents can interrupt these systems at specific points, enabling multiplication of microorganisms with resultant invasive pneumonia, chronic interstitial infection, systemic infection, or perhaps bacterial multiplication limited to the mucus layer within airway lumens. Moreover, an established infection may itself further compromise host defenses and lead to its own perpetuation (for example, bronchiectasis), or to a secondary infection with a different infectious agent (for example, staphylococcal pneumonia following influenza).

In the pathogenesis of infectious pneumonitis, exposure to environmental substances which are toxic to phagocytes, or the administration of immunosuppressive agents, is of primary concern because of reduction or loss of these host defenses. Resistance is further influenced by the presence of chronic disease in the lung or in other organs which may add metabolic abnormalities. Specific immunity to one or another of



the challenging microorganisms has a significant effect on the magnitude of impairment produced by environmental toxic agents or host disease processes.

Some infections, such as pneumococcal pneumonia, are characterized by a remarkable orderly sequence of events: pulmonary edema; containment within lung segments or lobes; cellular recruitment; and finally orderly removal of reaction products from alveoli to restore structure and function to normal. Other infections, such as that by influenza virus, have a rampant pulmonary edema phase which may never progress to a significant cellular phase. Still others, such as tuberculosis, follow the pneumococcal pattern, but instead of removal of debris and resolution, go onward to attempted storage of cell products, producing necrosis and sequestration by caseation and fibrosis.

The monitoring and regulation of the transition between stages of inflammation appear to be host-determined. Clearly this cascade of response must be studied and the contribution of infective agents, environmental cofactors and the many components of the host's defense system determined.

The relationship between cellular immunity in the lung and resistance to intracellular organisms has received inadequate study. Changes in cellular hypersensitivity may occur on exposure to environmental agents and in response to acute and chronic diseases which do affect the lung primarily. The major questions are how the known immune mechanisms control and modulate inflammation and whether there are other mechanisms still unknown.



The integrity of the lung depends upon connective tissues, including collagen, elastin, reticulin, smooth muscle, and the ground substance of interstitial space, which is rich in hyaluronic acid. Inflammatory responses may cause disease because of atrophy (emphysema) or metaplasia (fibrosis) of connective tissue. Those pneumonias which fail to resolve either digest the architectural framework of the lung or stimulate fibrosis. As little is known about the mechanism controlling these responses or the stimuli which elicit them, connective tissue changes after injury warrant study.

Viral infection sometimes impairs and delays peripheral lung clearance. Chronic pulmonary diseases which damage the alveolar and bronchiolar levels of the lung may delay clearance and thus lead to long-term storage of particles in the distal lung. This may permit colonization by infectious agents and ultimately infection and disease. Documentation as to whether clearance compartments exist in the peripheral lung and what mechanisms influence clearance rates and clearance compartments is a prime area for research. It should then be determined whether defects in defined phases of particulate clearance are correlated with specific forms of infectious pneumonitis and other chronic bronchopulmonary disorders.

The development of models could contribute to an understanding of many of these problems. The mammalian lung is not accessible for direct observation and manipulation. Furthermore, it is difficult to visualize because of the unique air-fluid interfaces. Better models and more knowledge of their uses and limitations would enable better understanding of the various functions of the lung both in vitro and in vivo.



Therapy

Approaches to viral diseases, especially influenza, should include consideration of newer vaccines, assessment of non-specific immunoprophylaxis, accelerated investigation of antiviral agents, programs for making such agents available, and improved methods of supporting patients with acute pulmonary insufficiency due to influenza. In vaccine trials for pneumococci it is essential to ascertain whether the ecological vacuum created will be filled with other types of pneumococci and whether these have similar degrees of potential virulence.

While there is an ongoing controversy regarding the efficiency of vaccination for tuberculosis, there is no question that alternative approaches to chemoprophylaxis, including immunoprophylaxis, should be considered. Areas of potential value include the use of purified immunogenic components and the use of substances such as "transfer factor." Investigation to determine the shortest and most effective chemotherapeutic regimen for tuberculosis should be carried out.

2.7.4 Recommendations

Investigations of lung defense mechanisms, by studying the component parts of clearance independently and with model systems where all components must function together are an essential first step to understanding the pathogenesis of infectious respiratory diseases.

Studies should be addressed to mucociliary transport of infectious agents; characterization of abnormal and normal

mucus, and the role these play in the clearance of infectious organisms; lymphatic pathways; the role of the lung phagocytosis in defense mechanisms; the role of local and circulating immunoglobulins together with investigations of cellular immunity to infectious agents. Lung surfactant should also be studied for its role in maintaining the lung free of microorganisms. Interaction of the above factors with the environment will be of considerable importance.

Moreover, it is important to determine whether lung tissue differs in its response to infectious agents depending upon the hosts. Furthermore, it is important to launch epidemiologic studies of host and environmental factors which modify the responses to infectious agents, and of alterations in the cellular and immunological defects which allow colonization of ill patients with unusual organisms. Such epidemiological studies should determine the characteristics of patients with a high incidence of infection, as well as the interaction of host factors, occupational exposure, and infection. It is also of interest to determine whether host factors are altered by atmospheric exposure or infection and whether host factors involving immune deficits allow ill patients to become colonized with unusual infectious agents. It is important to study the relationship of colonization of the upper and lower respiratory tract by similar or dissimilar organisms, the regional variations in the immunological reaction, the cell adherence of infectious agents, and finally, the interrelationship of the routes of clearance of infectious organisms in these portions of the lung.

The incidence and etiology of the immunodeficiency diseases should be investigated through the use of controlled prospective epidemiologic studies. These specific diseases include



humoral and cellular immunity defects; and the study of some humoral and cellular defects will generate much understanding into man's basic immunologic system. Investigation into lymphocyte function, lymphocyte membrane characteristics, mediators of cellular immunity, humoral immune response, and their genetic mechanisms in immunodeficiency disease is very important.

With regard to detection and diagnosis, an effort should be made to find more direct means of diagnosis of infectious agents responsible for specific diseases. Factors indicating tissue invasion as compared to surface colonization should also be identified. This should be accomplished by rapid diagnostic techniques involving, for example, immunofluorescence or negative staining in the electron microscope.

It is also important to develop a mandatory reporting system to determine the magnitude of fungal diseases in the American population. Moreover, specific fungi should be identified, and properties which enable them to colonize humans described.

Recently, non-bacterial, non-viral agents, such as *Pneumocystis carinii*, have become important and it would be reasonable to study why immunologically incompetent individuals are infected by such organisms. This can best be done by developing mandatory case reporting systems and by studying the gross characteristics of such organisms. It is also important to better define the etiological agents responsible for respiratory syndromes of the upper and lower airways in children, together with refinement in current diagnostic techniques. Thus, refinements of current techniques to define bacterial, viral, and mycoplasmic infections or



colonization in small airways will be important. Applications of new modalities such as organ culture, co-cultivation etc., should also be applied in these diseases. Methods should be sought to determine why different viral agents localize at different sites in the airways and to determine the role of maternal antibodies in the adult.

Early, accurate, simple means for detection and diagnosis of immunodeficiency disease is important. Development of screening services for study of cord blood lymphocytic and phagocytic functions should aid in this early recognition. Uniform screening tests for antigens in the assessment of cellular immune functions should be developed. More research is needed in order to develop accurate and sensitive methods for detecting immunodeficiency disease.

In terms of treatment and management, it is important to study the management of infectious diseases by means of immunoprophylaxis. This can best be done in such diseases as pneumococcal pneumonia or influenza by purifying the immunogenic components of tuberculosis vaccines, and, above all, by restoring immunologic competency, both cellular and humoral, to individuals with acquired or inborn deficiencies of the immune system. New approaches to therapy are required in the specific areas of antiviral agents, antifungal agents, anti-tuberculosis agents, and agents active against resistant bacteria.

A major thrust towards the development of antiviral agents should be a high priority item at this time. Moreover, it is important to develop newer, much less toxic antifungal agents as well as antimicrobial agents active against resistant



bacteria. To advance therapy for tuberculosis, it will be important to determine what the shortest possible treatment regimen is for this disease.

For rehabilitation, the long-term benefits to the patients and society of physical therapy, occupational therapy, and psychological therapy following severe or prolonged infectious disease should be investigated in a quantified fashion. The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.

2.7.5 Summary

Although significant advances against infectious diseases of the lung will be made by research directed at specified disease entities, the most productive results will not be obtained solely in this manner. Specific therapy may cure acute manifestations of illness, but in many instances this is only after permanent damage has occurred to the lung. Moreover, man must continue to live in an environment of microorganisms which will gain access to the lung. The most promising approach is through elucidation of the mechanisms by which the body defends itself against such invading microorganisms. Important host defense mechanisms that warrant investigation include the mucociliary transport system, the alveolar macrophage and immune systems, surfactant, and mucus. In addition to studies on the infectious agents, it is necessary to focus on host factors as well as on the interplay between infection and environmental factors.



Most host factors appear to modify the usual effects of infectious agents. Such host factors include age, sex, race, and genetic contributions. Specific metabolic diseases (such as diabetes mellitus or cystic fibrosis) as well as immunologic diseases (such as multiple myeloma) also accentuate the effects of infectious agents. The defensive roles of cells and mucus in the airways may be affected and changed by the menstrual cycle. Well-designed population studies are needed to provide clues to host factors involved in the development and cure of infectious pneumonitis.

Currently, most studies of environmental factors are simple toxicity studies of single agents on one mechanism of host defense. But other factors are believed to be important. These include obesity, alcoholism, vitamin A deficiency, and toxic chemicals. Occupational exposure to mineral and organic dusts are important cofactors for a few infectious pulmonary diseases. Low socioeconomic position, with all it implies, also clearly needs study as a complex cofactor.



2.8 SARCOID AND GRANULOMATOUS LUNG DISEASES

2.8.1 Introduction

Granulomatous diseases of the lung of unknown etiology include sarcoidosis, Wegener's granulomatosis and eosinophilic granuloma, but only the first of these has a significant incidence. Sarcoidosis has histologic features resembling those of mycobacterial and fungal infections, while the response to cytotoxic drugs in Wegener's granulomatosis and eosinophilic granuloma resembles that of neoplasms. The three diseases have little pathologic resemblance and differ in epidemiologic and immunologic characteristics.

Sarcoidosis has been widely investigated without success in determining etiology or in producing a model in experimental animals which resembles that seen in man. Most patients have been found to show a disturbance of delayed hypersensitivity, a seemingly non-specific increase in certain circulating antibodies, and transient or prolonged reactivity to the Kveim antigen.

The pathologic features in Wegener's granulomatosis and eosinophilic granuloma suggest that immunologic processes are involved in these diseases.

2.8.2 Magnitude of Problem

Although only sarcoidosis is sufficiently prevalent to constitute a national health problem, all three disorders have considerable economic consequences because they occur in early and middle adult life. Sarcoidosis is more common in

women, and is 12 to 15 times more common among blacks. The disorder may affect all parts of the body, but serious damage is most commonly pulmonary where it may contribute to severe disability. The disease varies remarkably; at one extreme it causes no symptoms, is detected only by chest X-ray surveys and lasts only a few months; thus, the frequency of persons affected may considerably exceed the number recognized. These attacks may, however, permanently affect certain immunologic defense reactions; thus, the unrecognized cases are not inconsequential. Several studies indicate that a third of the more severe cases require treatment with corticosteroids, and among these, disability and death are not uncommon. Progression may occur despite early diagnosis and prompt therapy.

Sarcoidosis now outranks tuberculosis, particularly among blacks, as a cause of disability due to pulmonary insufficiency. Mortality data are not reliable since, in the past, deaths from sarcoidosis were often attributed to tuberculosis.

The other granulomatous disorders are less common. The pulmonary form of eosinophilic granuloma exhibits an even more restricted age prevalence than sarcoidosis and is recognized most often in young men. Wegener's granulomatosis represents a disorder which until recently appeared to be almost invariably fatal; no ethnic, sex, or age pattern of occurrence has been observed in it.



2.8.3 Current State of Knowledge

Etiology

Sarcoidosis has an uneven distribution, with greatest frequency in Northern Europe, the United States, and Australia, and least frequency in underdeveloped countries. It is uncertain whether environmental or geographic factors or variations in diagnostic resources are responsible for the differences in distribution. A recent study suggests that ethnic factors are more important than environmental ones. Detection of a genetic or environmental factor common to seemingly disparate populations should provide an important clue to the cause of the disease.

It would be of interest to determine the host characteristics of subjects prior to the onset of sarcoidosis, and the occurrence in patients and controls of allergic and immune disorders, infections, (viral, bacterial and fungal) neoplasm and autoimmune diseases. Such studies should include measurements of antibody responses to immunization and delayed hypersensitivity. Among the population groups which should be studied are the offspring and younger siblings of patients with sarcoidosis, and student nurses and medical students since these groups have a higher likelihood of recognition of sarcoidosis. It would be desirable to examine comparable ethnic groups in the rural South and urban North to determine possible effects of air pollution and other regional differences. There should be further study of familial occurrence, and an attempt made to determine whether the concentration of sarcoidosis in the third and fourth decades is a reflection of constitutional factors or of exposure to extrinsic agents.

Although microbiologic investigations have revealed little evidence that sarcoidosis is an infectious disease, belief in a relationship to mycobacterial infection persists. Tuberculosis is no longer the common complication it was, and the failure of sarcoidosis to decline in incidence as has been the case in tuberculosis suggests that the latter is not an etiologic factor. Recent electron microscopic studies indicate that tuberculosis-like structures found in sarcoid lesions are not mycobacteria.

Pathogenesis

The altered immunologic characteristics resemble in certain respects those in certain other chronic inflammatory diseases affecting various organs. In none of these, however, is there the pattern of granulomatous response to intracutaneous injection of Kveim test suspension. Moreover, there is neither impairment of delayed hypersensitivity nor such a consistent increase in antibody responses to certain viral antigens.

Despite anergy or impaired delayed hypersensitivity, regarded by some to be due to an abnormality of the T-lymphocyte system, the lymphocytes in sarcoidosis patients are sensitive to antigens in vitro. An increase of circulating blocking antibodies has been postulated. The anergy has been attributed to an inability to remember sensitivity, rather than to an inability to develop it.

Studies of transfer of cellular hypersensitivity are of special interest. A recent observation has shown that "transfer factor" transmitted from nine patients with tuberculoid



leprosy to cases with the lepromatous variety resulted in the prompt appearance of erythema nodosum or arthralgia in four cases. Erythema nodosum and sarcoidosis are commonly associated in North Europeans, less often in Puerto Ricans and infrequently in mainland Americans. The course of sarcoidosis is usually more benign in patients who have erythema nodosum. An explanation of the genesis of erythema nodosum in immunologic terms should contribute greatly to our understanding of sarcoidosis. It would be most informative to ascertain whether administration of transfer factor from Kveim-positive to Kveim-negative patients would induce reactivity. Conversely, if transfer factor from Kveim-negative cases abolished the reaction in Kveim-positive cases, therapeutic benefits might be anticipated.

Clinical Aspects and Obstacles

Diagnosis is accomplished with a reasonable degree of accuracy in cases of sarcoidosis by tissue biopsy. On the other hand, an immunologic diagnostic test would provide a significant reduction in hospitalization costs. It is possible that isolation of a specific factor in Kveim test preparations would aid in determining the cause of sarcoidosis. Unfortunately, there are problems in the preparation, standardization and interpretation of Kveim test materials. No single suspension is widely available to investigators, and different lots differ in their behavior.

Uncertainty regarding the diagnostic specificity of the Kveim reaction has interrupted promising progress toward development of in vitro methods of diagnosis of sarcoidosis. An obstacle to identification of a specific antigen in test



materials has been the finding that the active agent appears to reside within the subcellular particles of the test suspensions. It has been suggested that these represent exogenous material phagocytized by epitheloid cells.

There is general agreement regarding presently available methods of treatment. Patients without symptoms and lymph node involvement are not treated; corticosteroid therapy is useful in suppressing inflammatory changes in patients ill with fever and visceral manifestations.

The value of corticosteroid therapy in patients whose symptoms are minimal but who have persistent pulmonary infiltrations is under debate. The superiority of cytotoxic or immunosuppressive drugs in Wegener's granulomatosis and eosinophilic granuloma over corticosteroids suggest the advisability of further trials of these agents in sarcoidosis.

Models

Efforts to produce a satisfactory model of sarcoidosis in experimental animals have been unsuccessful. Several investigators have produced local granulomas resembling sarcoid at the sites of injection of irritants. Guinea pigs and dogs receiving injections of Freund's adjuvant and similar substances have shown transient pulmonary granulomas. In none of these studies has a disease resembling generalized sarcoidosis been produced.

2.8.4 Recommendations

It is important for the prevention of sarcoid to determine the existence of external or intrinsic factors which

contribute to its peculiar racial prevalence and geographic distribution. This may be done by selecting black populations at risk in high incidence areas and comparing applicable qualities and factors with those of low susceptibility populations (white) in the same area, and comparing the existence of the same qualities in two racial groups which dwell in a low incidence area. These investigations may be addressed to the genetic, dietary, and environmental factors, as well as to antecedent "triggering" diseases. It is also important to study variations in antibody response following immunizations in these populations.

There is need to determine underlying or preexisting alterations in delayed-type hypersensitivity involving in vitro lymphocyte activity, the role of the various mediators of cellular hypersensitivity, and the mechanism of the foreign body reaction in patients with sarcoid.

In order to plan appropriately, certain institutions with high access to patients with sarcoidosis would provide opportunities for in-depth multidisciplinary studies of the disease; the experience thus garnered could provide consultation and assistance to other institutions. Such centers could be responsible for the storage and distribution of standardized cells, tissues and serum of patients with authenticated sarcoidosis. They could also act as repositories, evaluating agents, and distribution points for data and tissues from patients with other pulmonary granulomatous diseases resembling sarcoid.

In the investigation of sarcoidosis, we need to develop animal models for the experimental induction of similar



disorders utilizing a variety of species under different experimental conditions. One may utilize a broad spectrum of biologic or other agents in the intact or immunologically altered animal in order to find a susceptible host. Among the agents so used should be the so-called slow viruses. It should also be possible to modify the immunogenic qualities of the agents used as well as the immunologic capacity of the recipient host.

With regard to detection and diagnosis, prolonged follow-up studies of patients with sarcoidosis are required in order to delineate the course of the disease and its sequelae. Either in single centers or by the receipt of follow-up data from different institutions, statistical probabilities can be determined, especially as these relate to the lung in untreated cases and those receiving various forms of therapy.

The frequency of spontaneous subsidence or resolution, the frequency and character of the sequelae, and the effects of various therapeutic modes and their predictability can then be appropriately assessed. It will be especially important to clarify the relationship between "childhood sarcoid" and the adult form of the disease.

It is highly desirable that the production and effectiveness of the Kveim antigen be improved or a superior substitute for it be found. Using newer methods of preparation, the chemical nature of the antigen should be clarified. Indeed, a non-invasive substitute for the Kveim test, perhaps an in vitro method, would be highly desirable.

Clinical trials for the treatment of sarcoid lung disease should be initiated under carefully controlled conditions to

determine the comparative efficacy of various forms of therapy. Among these, one might determine the efficacy of cross-administration of transfer factors between Kveim-positive and Kveim-negative patients or determine the therapeutic efficacy of immunosuppressive drugs.

Long-term clinical studies should feature studies of disease progression or regression following both continued and discontinued steroids.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.

2.8.5 Summary

Sarcoidosis and other granulomatous lung diseases currently represent a significant national health problem. Sarcoid, which is much more prevalent than other granulomatous lung diseases, is 12 to 15 times more common in blacks and currently outranks tuberculosis as a cause of pulmonary insufficiency. Approximately one-third of the cases are severe enough to necessitate corticosteroid therapy, and disability and death are not uncommon. In order to better define this disease process as well as other granulomatous lung diseases, further investigation with epidemiologic studies and animal models is necessary. More research is needed in terms of early diagnosis, especially with the Kveim reagent, and therapy.

2.9.1 Introduction

This Problem Area includes hypersensitivity pneumonitis (extrinsic allergic alveolitis). It is a diffuse interstitial granulomatous lung disease due to an allergic reaction following inhalation of a specific organic dust. The disease syndrome should be suspected in all patients with recurrent fever, chills, cough, and dyspnea; chronic unexplained cough, sputum production and dyspnea; and in patients with symptoms suggestive of chronic pulmonary fibrosis. Wheezing may occur, but is unusual. In the typical acute form of hypersensitivity pneumonitis, episodes of fever, cough and dyspnea occur four to eight hours after exposure to the antigen. In its chronic form, the disease results from continuous or repeated exposure. Although the roentgenographic and pulmonary function abnormalities are not specific, the majority of patients have serum-precipitating antibodies against the specific offending antigenic dust (when it can be identified). However, these antibodies can also be detected in the serum of up to 40 percent of exposed, but presumably well, individuals.

Some forms of infiltrative pulmonary disease, characterized by restrictive or obstructive pulmonary dysfunction, may overlap with hypersensitivity pneumonitis as defined above. These include the following:

- Allergic bronchopulmonary aspergillosis. In spite of primary obstructive dysfunction, these patients present evidence of infiltrative pulmonary disease.



- Pulmonary manifestations of hypersensitivity vasculitis, "rheumatoid lung," lupus erythematosus, polyarteritis, and other likely hypersensitivity pneumonitides associated with administration of certain drugs (e.g., hexamethonium, nitrofurantoin).
- Certain idiopathic pulmonary diseases with or without associated systemic involvement (currently categorized as possible sarcoidosis, interstitial pneumonia or "idiopathic" pulmonary fibrosis).

Hypersensitivity is not characterized in statistical reports of incidences of respiratory diseases. In comparison with most other respiratory diseases, hypersensitivity pneumonitis does not contribute significantly to overall mortality. Because hypersensitivity pneumonitis has only been recognized as a disease for a relatively short time and since many of the antigens responsible for causing the disease may have been recognized by only relatively few physicians, it is safe to say that it will assume increasing importance among respiratory diseases.

2.9.2 Magnitude of Problem

Because of presenting symptomology, patients with hypersensitivity pneumonitis may be confused with patients with other inhalation diseases, interstitial diseases, or even diseases of the airways. As an example, it is difficult to estimate the frequency of Farmer's Lung. A collaborative study in 1964 reported that of 311 farmers with respiratory symptoms, 41 had precipitants to moldy hay. Patients came primarily from north central United States. In one county in Scotland, 7.8 cases per 100,000 were found in the general population, but among farmers the frequency was 110 per 100,000. In the



past ten years, over 200 cases of Farmer's Lung have been seen at a university center and another 200 at a large clinic in Wisconsin. One referral clinic still sees about 20 new patients a year, a frequency about the same as new cases of sarcoid.

Over 600 cases of Bagassosis are referred to in the literature and with approximately 500 in Louisiana. The disease is of worldwide distribution and occurs wherever sugar cane is processed.

It is noteworthy that following an outbreak of Maple Bark Strippers Diseases, changes were made in the operation of the paper mill and no new cases of the disease occurred. This underlines the public health value of recognition of a disease and identification of offending antigens. Industrial outbreaks can be controlled by proper manufacturing processes.

In a study of recent outbreak of hypersensitivity pneumonitis occurring in an office contaminated with thermophilic actinomycetes, all individuals were apparently exposed to the same amount of antigen and, when examined, revealed 15 percent of the exposed group became ill and an additional 35 percent developed precipitants without detectable illness.

Those who have had experience with hypersensitivity pneumonitis are convinced that the diagnosis is being missed and that it is more common than published figures would imply. The frequency of hypersensitivity pneumonitis due to antigens which have not as yet been identified is very difficult to estimate.



Although no definite statistics are available for deaths due to hypersensitivity pneumonitis, it is fair to say that morbidity rather than mortality is the major problem. However, deaths do occur: at least eight deaths have been reported due to Farmer's Lung and four deaths due to Bagassosis. Overall sequelae and complications of hypersensitivity pneumonitis appear to be those associated with chronic lung disease. A significant number of patients progress to chronic restrictive and/or obstructive lung disease without full recovery. This increases the need for hospitalization and outpatient medical care in such individuals.

2.9.3 Current State of Knowledge

Relatively little is known about the natural history of hypersensitivity pneumonitis; most of the information available is for two varieties of the disease: Farmer's Lung and Pigeon Breeder's Disease. Recognition of hypersensitivity pneumonitis as a distinct entity depends upon identification of the causative antigens. Several have been recognized, many others are suspected, and specific precipitating antibodies have been found in the sera of appropriate patients. The role of precipitants in the pathogenesis of these diseases is uncertain, but the diagnostic importance of their association with disease is generally recognized.

Demonstration of precipitants depends upon isolation of the specific antigen and the demonstration of antibody by immunologic techniques such as immunodiffusion. With the



advent of commercial gel-diffusion kits for demonstration of serum antiactinomycete and fungal and organic dust precipitants, there is now a clear need for standardization of antigens and techniques employed. The antigens presently recognized as causing hypersensitivity pneumonitis are encountered in organic dust with particles of about one to five microns. For sensitization, heavy exposures may be required followed by reexposure to small amounts to provoke symptoms in sensitized persons.

For screening purposes, a suspected dust should be checked for antigen content. Controls should be included such as healthy nonexposed persons and persons similarly exposed but not ill. Further identification requires culture of the dust for thermophilic and mesophilic molds and bacteria and preparation of antigens from these microorganisms. Recent recognition of hypersensitivity pneumonitis due to thermophilic actinomycetes growing in air conditioners and humidifiers indicates that, even if no obvious source of dust exists, the patient's environment should be cultured for a variety of microorganisms and extracts prepared from the predominant organisms. Final identification rests on close observation of the patient following return to the suspected environment during an asymptomatic period, and, if necessary, specific provocation of symptoms following aerosol challenge with the purified and identified antigen.

To advance knowledge of the hypersensitivity lung diseases, however, it is important to emphasize that serum precipitants may be absent when the disease is not in an acute phase and some symptomatic individuals may develop precipitants without overt hypersensitivity pneumonitis. False



negative tests are frequent, usually because antigens are of insufficient potency and purity. Several types of false positive precipitant reactions may occur.

Provocative challenge as a diagnostic method is not without hazard and cannot be recommended as a routine procedure. Considerably more work is needed to standardize and evaluate the place of provocative challenge in the diagnosis of these diseases.

The lung defends itself and the body from inhaled materials by various means, but very little is known of the role played by immunological mechanisms in this defense. To what extent these mechanisms are protective, to what extent destructive, and what factors determine these alternatives require elucidation.

Little is known regarding conditions required to stimulate an immune response to inhaled antigens. The role of cell-mediated (delayed) hypersensitivity in hypersensitivity pneumonitis is presently unknown, but it appears to account for acute lesions in experimental animals bearing histopathologic resemblance to the spontaneous disease in man. Little has been learned as yet about the handling of inhaled antigen in the subsequent development and versatility of the immune response in experimental animals.

Additional problems arise when attempting to collect and standardize samples from patients, due to the limitations of obtaining material from human lung by invasive techniques.



2.9.4 Recommendations

At present, recurrent attacks of hypersensitivity pneumonitis can be only prevented by avoidance of exposure to specific antigens. Neither prevention nor effective treatment can be achieved until the pathogenesis of these diseases is elucidated. Because of obvious difficulties in extensively studying humans, the most promising approach to an understanding of the pathogenesis of hypersensitivity pneumonitis is through animal models. Elucidation of pathogenetic mechanisms in animal models may contribute to the development of more consistently reliable tests of diagnosis of hypersensitivity pneumonitis.

Basic problems that should be addressed include mechanisms by which inhaled antigens produce an immunogenetic response; the role of humoral and cellular mechanisms in the production of various pulmonary lesions; and the effects of immunoglobulins and biological activity on hypersensitivity reactions.

Procedures are available for screening suspected dusts for antigen content, but final identification rests on closer observation of the patient when exposed to the suspected environment. In some instances, provocative challenge by the antigen is necessary for definitive diagnosis.

Studies are needed to explore the adaptability of more sensitive uncomplicated gel-diffusion techniques, such as counter immunoelectrophoresis, to demonstrate serum precipitins. Standardization is necessary to permit comparison on a national basis of antigen sources for gel double diffusion



studies. Such standardized preparations are necessary to evaluate the role of provocative challenge in the diagnosis of hypersensitivity pneumonitis.

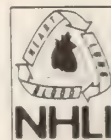
Studies of the natural history of hypersensitivity pneumonitis are necessary for more effective diagnosis and treatment of these diseases. Long-term follow-up studies of known cases with different etiologies are necessary to assess the effects of long-term exposure to, or avoidance of, various antigens. These studies are also necessary to develop more specific and more sensitive screening tests as well as to characterize the immune mechanism involved in the perpetuation of, or recovery from, these diseases.

Additional work would revolve around discovery of new antigenic dusts producing hypersensitivity pneumonitis as specific clinical entities and should employ the same approaches outlined above.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.

2.9.5 Summary

Hypersensitivity lung diseases represented mainly by Farmer's Lung, Pigeon Breeder's Disease and Bagassosis are not rare diseases. It is possible that a good deal of acute recurrent respiratory disease is due to hypersensitivity to lung diseases. Little is known about the natural history of hypersensitivity lung diseases and research concerning serum



precipitations is not very far advanced. Investigation into pathophysiology, patterns of incidence and longitudinal studies of natural history are necessary. Simple, accurate means for diagnosis should be developed and treatment should be centered around avoidance of antigen with development of antiinflammatory therapy and therapy to counteract immunologic (IgG) reaction to antigen.



2.10 PULMONARY VASCULAR DISEASES

2.10.1 Introduction

Cor pulmonale, pulmonary hypertension and pulmonary edema are vascular disorders addressed in the Problem Area.

Cor pulmonale is cardiac enlargement resulting from diseases primarily affecting either the structure or function of the lung. A large number of diseases affecting the pulmonary circulation imposes a chronic increase in workload on the right ventricle that may result in hypertrophy and ultimately right ventricular failure. Conditions primarily affecting the ventilatory and respiratory functions of the lungs, or conditions acting directly on the pulmonary vessels are potential causes of cor pulmonale. Certain congenital heart lesions, and conditions primarily affecting the left side of the heart, may also exert secondary effects on the lung, but such conditions are excluded as causes of cor pulmonale by the Panel's definition. Right ventricular hypertrophy is the only lesion that is common to all patients at all stages of cor pulmonale.

Subjective evaluations of ventricular hypertrophy or assessments by measurement of mural thickness are unacceptable because minor degrees of hypertrophy may be masked by cardiac dilation and it is impossible to compare observations made by different observers. It is essential to employ the more exact method of dissecting the ventricles apart and weighing them separately. The criterion for right ventricular hypertrophy based on this technique is a right ventricular weight

of 80 grams or more. The criterion for left ventricular hypertrophy is a left ventricular weight greater than 225 grams.

Pulmonary hypertension is characterized by the elevation of pulmonary arterial pressure markedly above levels usually accepted as normal. A definitive diagnosis can be established only by right heart catheterization.

Elevation of pulmonary arterial pressure in the absence of cardiac or pulmonary diseases that might cause the elevation is called "primary" or "idiopathic" pulmonary hypertension. Experienced pathologists are often able to distinguish between cases of vasoconstrictive primary pulmonary hypertension that has been complicated by thrombosis and cases of secondary pulmonary hypertension which are due to thromboembolism.

Primary pulmonary hypertension is found in women with Raynaud's phenomenon and who frequently develop scleroderma; persons at high altitude who are exposed to low oxygen; and persons who have ingested certain drugs and chemicals. Oral administration of plant alkaloids to rats and monkeys leads to severe pulmonary hypertension and death from right ventricular failure. A recent epidemic of primary pulmonary hypertension in Europe has been ascribed to ingestion of an appetite-suppressing drug, Aminorex, but it has not been possible to duplicate this condition in experimental animals.

Secondary pulmonary hypertension may be the consequence of obliteration of the pulmonary vascular bed in lung diseases,



passive elevation of pulmonary arterial pressure because of congestive heart failure or pulmonary edema, elevation of pulmonary blood in certain congenital heart diseases, alveolar hypoventilation, and neurogenic or humoral pulmonary vasoconstriction, as in certain cases of mitral stenosis.

Pulmonary edema is a pathologic state in which there is abnormal extravascular storage of fluid in the lung. With the methods presently available, pulmonary edema can only be detected clinically late in its course, making prompt therapy of the developing condition impossible, and contributing to its morbidity and mortality.

In this report only pulmonary edema consequent to pulmonary capillary or left atrial hypertension is considered.

2.10.2 Magnitude of Problem

Accurate figures are unavailable on the national incidence of cor pulmonale or on its associated morbidity and mortality. However, a clue to its impact on national health may be found in the fact that chronic bronchitis and emphysema are the major causes of cor pulmonale and these two disorders are very common. The frequency of its occurrence in these diseases is not accurately known, but it may be estimated that cor pulmonale occurs in 40 percent of cases of emphysema and chronic bronchitis.

Hospital autopsy records vary in the reported prevalence of cor pulmonale from 0.9 percent of all cardiac autopsies in Massachusetts to 54 percent in Arizona. Data from clinical discharges and autopsy services at three hospitals indicate



that cor pulmonale might be present in 0.4 percent of discharges. Extrapolating to the 30,814,830 hospital discharges in the United States during 1969, there might be 123,000 cases of cor pulmonale.

The prevalence of primary pulmonary hypertension is certainly underestimated because the diagnosis can only be established by right heart catheterization. It is noteworthy that many patients studied by right heart catheterization show clinical features strongly suggestive of pulmonary hypertension. In one study, primary pulmonary hypertension was found in 0.5 to 1 percent of right heart catheterizations and anatomic evidence was found in 0.15 to 0.2 percent of autopsies.

The frequency of pulmonary edema is undoubtedly underestimated. It is not reported if it occurs during hospitalization and is coded only when reported as the admitting diagnosis. Moreover, many patients with mild pulmonary edema are treated in emergency rooms or at home. As cardiogenic pulmonary edema is mainly the consequence of either degenerative or rheumatic cardiovascular disease, estimates of the magnitude of the problem of pulmonary edema in terms of national health must take into account those cardiovascular diseases with which it is associated. Degenerative cardiovascular disease is the major cause of death in the United States today, and the complication of pulmonary edema undoubtedly contributes significantly to this mortality.



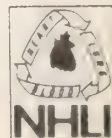
2.10.3 Current State of Knowledge

Detection and Diagnosis

Assessment of pulmonary circulation by cardiac catheterization is not practical for screening early cases of pulmonary hypertension or for serial examination of established cases. More practical, noninvasive techniques are under investigation in a number of centers. The most promising technique for indirect measurement of pulmonary arterial pressure is the nitrous oxide plethysmographic determination of instantaneous pulmonary capillary blood flow. Conduction time of the pulmonary arterial pulse bears an inverse relationship to mean pulmonary arterial pressure. The method gives a very high correlation between calculated and measured mean pulmonary arterial pressure.

Other techniques which might permit indirect estimation of pulmonary arterial pressure by measurement of pulmonary arterial conduction time include fluorodensitometry and gamma densitometry. By these methods, regional ventilation of areas as small as 3 cm in diameter can be estimated.

Measurement of pulmonary arterial blood volume is helpful in determining the presence of active or passive alterations in pulmonary vasomotor tone when pulmonary blood flow also is altered by a pharmacologic stimulus. Its measurement in man has been accomplished by a method requiring the injection of an ether solution into the pulmonary artery, but a less invasive technique which shows promise is injection of a gamma-emitting isotope into a vein and following of its time-course



by a scintillation camera. The value obtained with these methods is similar.

With regard to pulmonary edema, the critical problem at this time is detection early enough in its course to be amenable to treatment. Physical or chest roentgenographic examinations detect pulmonary edema only at a late stage. Even such sophisticated procedures as estimation of extravascular pulmonary water by indicator dilution are insensitive to the early accumulation of fluid. Under light microscopy, the earliest manifestations of excess fluid in the lungs are in the connective tissue that surrounds small vessels and airways. When widening of alveolar septae can be visualized by light microscopy, it is a late manifestation of pulmonary edema. If lung water content could be accurately measured, it might be used to detect early pulmonary edema, but methods presently available are too insensitive or too cumbersome to employ in clinical situations.

The simultaneous determination of the pulmonary blood volume and the pulmonary extravascular water volume is an invasive technique not technically suitable for widespread clinical use. Promising new techniques are being investigated.

Pulmonary tissue volume, which parallels the extravascular pulmonary water space, can be estimated by various techniques. But the procedures presently available are too complicated for use in patients with pulmonary edema.

Another potentially useful technique to assess increases in lung water is estimation of transthoracic electrical

impedance. However, although simple conceptually, technical difficulties have precluded its clinical application.

Pathophysiology

As cor pulmonale is most frequently a consequence of chronic bronchitis and emphysema, studies of its pathogenesis will draw upon what is known about pathophysiology of chronic obstructive lung disease and emphysema.

For some years, it has been suspected that the left ventricle may also be involved in responses of the heart to lung disease. Autopsy studies suggest an increase in left ventricular wall thickness. Patients have shown clinical, radiological, and hemodynamic evidence of left ventricular dysfunction in the presence of severe lung disease. Because the majority of patients with cor pulmonale are middle-aged or elderly men, there is frequently coexistent systemic cardiovascular disease which may not be clinically evident. Left ventricular dysfunction in such patients may have a multifactorial basis.

There is still uncertainty and debate as to whether chronic hypoxia or reduction of the capillary bed is more important in the pathogenesis of cor pulmonale. This is a fundamental matter of practical importance since destruction of the pulmonary capillary bed is an irreversible lesion, whereas pulmonary vasoconstriction as a consequence of hypoxia is potentially reversible. This emphasizes the need to use pathologic methods that permit a quantitative approach. It is essential to employ modern morphometric methods. Although



available, these methods are not used widely enough. Methods based on subjective grading of right ventricular hypertrophy and evaluation of emphysema are valueless. Quantitative histological methods should be used to measure the total internal surface area, number of alveoli, and number of capillaries in the lungs.

Promising clues to the pathophysiology of pulmonary hypertension are emerging from studies of the ultrastructural pathology and electrophysiology of smooth muscle. This has led to observations providing ultrastructural evidence essential to the development of a model of contraction in vertebrate smooth muscles. The possibility that hypertension (pulmonary or systemic) may be accompanied by ultrastructural changes (e.g., abnormal volume) of sarcoplasmic reticulum in vascular smooth muscle should be explored.

Electron microscopic studies of drug action on mitochondria and sarcoplasmic reticulum should provide greater insight into the mechanism of action of pulmonary vasoconstrictors and vasodilators as well as of bronchoconstrictors and bronchodilators.

Electrophysiological technical advances have included the introduction of extracellular and improved intracellular techniques for measurement of smooth muscle membrane resistance. Membrane electrical activity plays a major role in regulating smooth muscle contractility, and, if abnormal, may contribute to the pathogenesis of pulmonary and other hypertensive states.



Ion movements have been used to determine the effects of drugs on smooth muscle. An extension of such experiments to pulmonary vascular smooth muscle and to other forms of hypertension would provide information about possible abnormalities of membrane permeability.

With regard to pulmonary edema pathophysiology, studies of alloxan-induced pulmonary edema in the dog using tagged erythrocytes and albumin suggest that detection of protein rather than water in the lung might be a more sensitive early indicator of abnormality. Both red cell volume and albumin increase in the edematous lung, but protein accumulation seems to occur earlier than capillary congestion.

In normal subjects studied by indicator dilution methods, pulmonary capillaries are relatively impermeable to sodium ions during the first circulation. However, patients with pulmonary insufficiency following surgery or injury show a significant loss of sodium. This loss probably represents sodium entry into a slowly exchanging compartment and might be correlated with the extent of pulmonary capillary damage.

Lipid analysis of the alveolocapillary membrane has largely concentrated on the role of surfactant in promoting alveolar stability. Alterations of lipid composition of the membrane in pulmonary edema might also affect its permeability characteristics.

2.10.4 Recommendations

Prevention

Major advances in prevention of cor pulmonale would involve studies of normal cardiopulmonary function, identification and study of factors affecting cardiac function as a result of pulmonary parenchymal or pulmonary vascular dysfunction, and the development of measures which reduce or suppress factors associated with respiratory damage.

Prevention of pulmonary hypertension would require studies of the normal and abnormal cardiopulmonary structure and function, and additional studies of the pathophysiology of pulmonary hypertension including neural effects, endocrine effects, and electrolyte effects. Noninvasive approaches to the measurement of pulmonary artery pressure are needed.

Prevention of pulmonary edema requires studies of its pathogenesis including studies on water content of the lung and its compartmental distribution, metabolic activities of edematous lung, defense mechanisms in the edematous lung, characterization of endothelial and epithelial barriers, effect of various agents on the various cellular barriers, the role of pulmonary lymphatics, the role of surfactant, the clearance of lung liquid at birth, and studies of the composition of pulmonary edema fluid. The differences between cardiogenic and noncardiogenic pulmonary edema should be investigated. Additional studies for prevention include the nature of structural changes associated with pulmonary edema, studies of its clinical background, associated disorders, and the development of animal models.

Detection

Detection and diagnosis of cor pulmonale can be accelerated by the development of techniques for simple, accurate diagnosis of cardiac abnormalities; development of techniques for the simple, accurate diagnosis of pulmonary abnormalities; and extensive studies of the effects of hypoxia on cardiac function and the development of suitable animal models.

Detection and qualification of pulmonary artery pressure in large groups of normal subjects and patients with lung disease but without obvious evidence of pulmonary hypertension is needed.

The development of sensitive and accurate techniques is necessary to determine the presence and extent of pulmonary edema.

Treatment and Management

For cor pulmonale, treatment and management require clinical trials of presently available therapeutic approaches; studies of the roles of associated factors such as environmental pollution; evaluation of new drugs, such as pulmonary vasodilators; and the development of life support mechanisms in patients with extensive disease. Rehabilitation should include studies of long-term oxygen administration to patients with cor pulmonale related to hypoxemia and the effects of graded exercise.

A variety of vasodilators of potential value in therapy of pulmonary hypertension have been under investigation, but their therapeutic assessment has been hampered largely by the absence of appropriate noninvasive techniques for the assessment of pulmonary hypertension.

The effect of prostaglandins on pulmonary circulation has received scant attention despite extensive investigations of these compounds by numerous workers over the past few years. Beta-receptor stimulants recently introduced for the treatment of bronchial asthma also appear to have pulmonary vasodilator effects. If these agents or their analogs can be shown to be free of inotropic cardiac effect, they might be useful in treatment of pulmonary hypertension by virtue of the prolonged duration of their action.

Bradykinin, a naturally occurring polypeptide, has no direct effect on pulmonary vascular resistance in man. Animal models are required to test the effectiveness of existing and new modalities for treating both pulmonary hypertension and for the management of pulmonary edema. The development of clinical trials to study the efficacy of various procedures and theories in different clinical varieties of pulmonary edema should be considered.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.

2.10.5 Summary

Pulmonary Vascular Diseases, separated into cor pulmonale, pulmonary hypertension and pulmonary edema, are significant national health problems. Estimates have been made which place the prevalence of cor pulmonale at 123,000 cases resulting in an annual economic burden of \$200,000,000; the prevalence of pulmonary hypertension at 6,000 cases resulting in an annual economic burden of \$10,000,000; and, the prevalence of pulmonary edema at 300,000 cases resulting in an annual economic burden of \$250,000,000.

For all three aspects of pulmonary vascular disease considered (cor pulmonale, pulmonary hypertension, and pulmonary edema) the following approaches should be employed:

- Anatomical studies including electron microscopy and scanning microscopy
- Determination of the composition and arrangement of the altered portions of the tissues and comparison with the normal lung findings
- Study of altered metabolic activities and responsiveness of the different cell or tissue types specifically involved in the disease process under study
- Assessment in clinical situations of the altered physiological function (e.g., smooth muscle contractility, response to vasoactive materials, pulmonary blood flow resistance as well as pressures and flows)



- Development of appropriate experimental models in vitro and in animals to permit testing of hypotheses concerning pathogenesis and also of various modalities of treatment
- Study of the clinical problems as seen in patients
- Assessment of the effectiveness of current methods of treatment
- Development of new methods of treatment.

In studies of cor pulmonale, the development of noninvasive and nondestructive means of assessing the extent of right ventricular hypertrophy would mark a major advance in providing for a definite diagnosis. Direct measurement of ventricular wall thickness is unlikely to be accessible in vivo in patients and indirect measurements related to ventricular hypertrophy must be developed.

In studies of pulmonary hypertension, a simple means of measurement of pulmonary artery pressure is a highly desirable goal to permit early detection of the disorder. Of major importance to an understanding of the pathogenesis in the study of the characteristics and responsiveness of the smooth muscle of the vessels of the pulmonary artery and its smaller branches.

In studies of pulmonary edema, the fundamental question is the manner in which water and its dissolved solutes cross from blood to the lung tissue and accumulate there. Do all the constituents of the accumulated fluid of pulmonary edema cross by the same pathways or are there parallel pathways available to a greater or lesser degree to

different constituents? Of equal importance clinically is the problem of the rapid serial measurement of the excess lung fluid or of the same manifestation of its presence.

In addition to the general major attacks indicated above, fruitful information can be obtained in a number of other ways. Thus, in cor pulmonale and in pulmonary hypertension the additional strategies proposed include:

- Long-term studies of patients with established disease
- Determination of role, if any, of genetic factors
- Determination of environmental factors including air pollution
- Studies of different population groups (environmental, genetic, social, economic) to determine relative importance of indicated factors in pathogenesis
- Studies of efficacy of various modalities of treatment in short and long-term studies.

In pulmonary edema, additional strategies include the following:

- Study of specific types of pulmonary edema such as in: Shock lung, high altitude, "heroin" abuse
- Study of environmental factors (e.g., ozone) in the precipitation of pulmonary edema
- Development of the means of rapid, indirect assessment of pulmonary edema in a given patient (particularly useful in an intensive care unit type of situation)
- Study of the influence of factors other than hemodynamics in the development of pulmonary edema (infection, viral or bacterial, chemical injury, aspiration).

2.11.1 Introduction

Hyaline membrane disease (often called "respiratory distress syndrome of the newborn") is a disorder characterized by immaturity of the lung with respect to its ability to synthesize or secrete adequate amounts of pulmonary surfactant. It is nearly restricted to infants born before 37 weeks gestation, has its onset at birth, and leads to death or recovery within a few days. The lungs after death are poorly distensible, deflate completely at atmospheric pressure, and show extensive atelectasis, some edema, and have eosinophilic material (the hyaline membranes) lining some of the peripheral airspaces.

Although similar pathologic lesions may be found in adults after a variety of insults to the lung, such as influenza pneumonia, oxygen poisoning, and massive aspiration, the adult forms of "respiratory distress" are sufficiently different from that of premature infants to warrant separate discussion (See Problem Area 13, Acute and Chronic Respiratory Failure).

Other pulmonary disorders of newborn infants such as the Wilson-Mikity syndrome deserve study. In general, they can be approached by means similar to those specified for hyaline membrane disease, and hence are not listed separately.



2.11.2 Magnitude of Problem

A retrospective and prospective study of RDS in neonates, sponsored by the State of California in the years 1968 through 1970 showed that approximately one percent of all live babies developed neonatal RDS. In national terms, this means about 40,000 babies a year. Without specialized treatment, over 50 percent of these babies die. This mortality could be reduced to 42 percent in centers where specialized care was available, and could be further reduced to 10 percent in centers that were well-staffed, well-equipped, and used the newest techniques. Since approximately 75 percent of all neonatal deaths occur in premature babies, and since RDS is most likely to occur in premature neonates, if death from RDS could be reduced or eliminated, the infant mortality rate in this country might be reduced to a level among the best in the world.

With the increase in neonatal intensive care centers and evaluation of survivors, it is now apparent that morbidity as well as mortality is reduced among low birth weight infants. Major neurological sequelae have been documented in nearly half of surviving infants under 1500 grams birth weight born in the 1950's, but in less than 10 percent of these reported by Rawlings et al. born since the advent of the "neonatal intensive care." (Lancet, 1.516, 1971) Stahlman in Tennessee, Outubridge in Montreal and Tooley in California all report intact survival with increasing frequency as the result of meticulous care in the neonatal period.



2.11.3 Current State of Knowledge

Since the first clinical description of hyaline membrane disease in 1949, there has been ever-increasing interest in this problem which is nearly restricted to the prematurely born infant (under 37 weeks) in the first days of life. Careful observation of the clinical course, evaluation of cardiopulmonary function, measurements of metabolic changes and evaluation of the lesion at autopsy have marked the work of the past 20 years. Many hypotheses have been put forward to explain this problem, including aspiration, heart failure, intrauterine asphyxia and shock, a genetic predisposition, and an expression of biologic variation with respect to the timing of the capability of synthesis of the pulmonary surfactant. This latter hypothesis is now widely held and has provided a stimulus to much research in the last few years.

Although the factors regulating maturation of the lung are not well understood, it is evident that the clinical expression of hyaline membrane disease depends upon a deficiency in the pulmonary surfactant. Whether this is a primary problem, namely the immaturity of the lung with respect to surfactant synthesis and/or secretion, or whether the cells that are the source of the surfactant are in some instances compromised, the final common pathway to the expression of the disease is surfactant deficiency leading to atelectasis and hyaline membrane formation. The membrane itself consists of cellular debris as well as fibrinogen and other plasma products. It is located in the dilated terminal bronchioles or alveolar ducts, and overlies injured epithelial cells. The membrane itself is not there at birth but is acquired in



the subsequent hours; in the infants who recover from the disease, it is cleared by macrophage ingestion.

Much attention has been devoted to the management of the infants including correction of their metabolic derangements with the intravenous therapy, maintaining an optimal thermal environment to minimize oxygen consumption, early provision of calories by the intravenous route, and methods of improving oxygenation, principally artificial respiration with increased inspired oxygen concentrations. Techniques for monitoring the course of the disease have evolved which include the use of serial blood samples withdrawn from the umbilical artery for measurement of blood gases with micro-techniques, as well as serial roentgenographic evaluation, and in some instances measurement of pulmonary compliance.

It is assumed that the rate of reduction of mortality and morbidity in recent years relates to a combination of effects achieved by supportive measures. The maintenance of adequate blood flow and oxygenation to the brain are thought to be responsible for the reduction in the neurological sequelae among surviving low birth weight infants.

Recently research has been directed towards the possibility of the prevention of the disease by the acceleration of lung maturation in selected low birth weight infants. The studies of Liggins and Howie from New Zealand published in the October 1972 issue of Pediatrics give promise that infusion of glucocorticoids into the mother at least 24 hours before delivery may improve the survival of infants delivered at less than 32 weeks gestational age. These observations



on the effect of steroids on lung maturation follow studies in lambs and rabbits which establish that cellular differentiation can be accelerated and surfactant production made possible ahead of the usual time by the differentiation of alveolar type II cells. These studies with glucocorticoids give promise to regulating the hormonal environment of the fetus to favor lung maturation and postnatal survival. Other compounds will doubtless be found which may be more effective and less hazardous, and these are being actively sought in a number of laboratories.

2.11.4 Recommendations

The major approach to eliminating hyaline membrane disease would be to understand its pathogenesis and consequently work towards its prevention. Most of the proposals are in the area of prevention, and underscore heavily the necessity to know much more about the developing lung especially with respect to surfactant metabolism. Since the major pulmonary problems of the newborn, hyaline membrane disease, pulmonary hemorrhage, infection, and the Wilson-Mikity syndrome are all more common in low birth weight infants, it becomes self-evident that more knowledge about the immature lung is essential if we are to provide optimal care for these infants as well as seek methods of prevention of their problems. Another major approach is to define the population at risk. This approach leads to the possibility of further evaluating reported regional variations in the disease, the genetic component, as well as gaining insight into many facets of biologic variability. Obviously, the ultimate method of prevention of a disease of prematurely born infants is to prevent prematurity itself, a major goal which might involve combined obstetric and pediatric approaches. For example,



one would want to know about the maternal factors that predispose to prematurity and these include a number of social as well as medical considerations.

Important questions include morphometry of the immature diseased lung, biochemical abnormalities of proteins and lipids, ultrastructural changes and histochemical changes in alveolar cells and capillaries, biochemical events in developing lung--especially pathways of lipid synthesis relationship of brain intraventricular hemorrhage to lung disease and ways in which the immature lung repairs itself.

A method of designating the fetus at risk could under some circumstances allow a delay in the timing of delivery, the use of agents to accelerate lung maturation, or at least provision for neonatal intensive care of the infant at risk. One illustration of prenatal diagnosis is recently reported with respect to lecithin concentrations in the amniotic fluid. Such measures of assessment of fetal lung maturity would allow designation of at least some of the population at risk. Further means of evaluating the likelihood of fatal disease in the infant once born also deserve further evaluation. An illustration of such approaches is the role of cord-blood proteins and enzyme determinations in assessing subsequent risk of death from the disease.

An approach that involves both prevention as well as treatment would be the evaluation of the many supportive measures that have been advocated in the early neonatal period such as the role of maintenance of fetal blood volume, thermal environment, caloric intake, respirators and the like. A number of questions could be answered with the development

of suitable animal models. Prematurely born lambs and rabbits have been studied extensively and still provide useful information, but at this point it would appear more important to try to study the prematurely delivered primate. Among the questions that could be answered better with an animal model than in infants are possible deleterious effects of methods of acceleration of lung maturation.

In the area of treatment, the necessity for establishing criteria for optimal care and the continuing evaluation of it is of upmost importance. Among the more specific approaches to optimal care would be regionalization of perinatal care, evaluation of the best methods of transport of infants, and further evaluation through clinical trials of pharmacologic agents for circulatory support or acceleration of lung maturation.

An important project in the approach to evaluating the fate of survivors of hyaline membrane disease of the newborn will be long-term follow-up to study the incidence of late sequelae such as alterations in pulmonary and cerebral function. These sequelae should be correlated with varying prenatal and neonatal management. Also, the immune status should be evaluated in survivors. The evaluation of various rehabilitation regimens and the development of models of a comprehensive rehabilitation program are covered in Problem Area 2, Environmental Respiratory Diseases.

2.11.5 Summary

Hyaline membrane disease and other respiratory disorders of the newborn infant are the major cause of neonatal mortality.

Infant mortality in the country is approximately 20 per 1,000 live births. In other countries in the world it is as low as 11 per 1,000 live births. A 50 percent reduction in infant mortality is feasible with application of knowledge now at hand. A further reduction in mortality and morbidity can be expected. Insight into the causes of prematurity would then practically eliminate hyaline membrane disease--the leading cause of death in live born infants in this country.



2.12 CYSTIC FIBROSIS

2.12.1 Introduction

Cystic fibrosis is an inborn metabolic defect transmitted as an autosomal recessive trait. The disease is characterized by generalized dysfunction of exocrine glands resulting in a clinical picture consisting of recurrent pulmonary disease, pancreatic deficiency, and elevated sweat electrolytes. Although most homozygotes for this disease have substantially all of the manifestations of the syndrome, great variations exist in the degree to which a given patient is involved. This presentation will be limited to the pulmonary manifestations of the disease.

2.12.2 Magnitude of Problem

In the United States, cystic fibrosis is one of the main causes of chronic illness in children and young adults and accounts for most of the deaths in pediatric patients with chronic pulmonary disease. The incidence of the disease in the United States is approximately one in 2,000 live births; thus, 5 percent of the general population in America must be carriers for the gene.

2.12.3 Current State of Knowledge

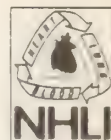
The basic defect in cystic fibrosis is not known. At present no one hypothesis reconciles all the diverse observations noted in this disease. Any proposed hypothesis would have to provide a unified and reasonable explanation of the sweat defect and associated abnormal mucous secretions.



Recent evidence from cell cultures of fibroblasts obtained from patients with cystic fibrosis gives experimental support to the hypothesis that all the cells reflect a basic biochemical defect. Several other investigators have observed that tissue culture cells from cystic fibrosis patients and heterozygotes accumulate increased quantities of acid mucopolysaccharides and glycogen. However, no basic defect has been identified in these cell studies. Recently, it has been noted that fibroblasts obtained from homozygotes in parents of children with cystic fibrosis have undermethylated RNA.

A ciliary motility factor has been demonstrated in the serum and saliva of homozygotes and heterozygotes for the cystic fibrosis gene. Initial attempts for isolation have shown association of the factor with the gamma globulin fraction of serum. More recently, cultured skin fibroblasts and leukocytes have been shown to produce and secrete the factor into the culture media. The chemical nature, origin and site of action of the factors have not been identified. Of great interest are the observations that the saliva or sweat from patients with cystic fibrosis introduced by retrograde injection into the parotid glands of rats or isolated sweat ducts inhibit sodium reabsorption. Basic mechanisms responsible for the inhibitory effect on sodium transport remain unknown.

The sweat electrolyte abnormality is present from birth and is unrelated to the severity of the disease. The sweat test is not elevated in the heterozygote for this disease and today no definite tests for the detection of the heterozygote state is available.



Chronic pulmonary involvement usually dominates the clinical picture and determines the fate of the patient. The initial lesion in the lung is bronchial obstruction which results from altered bronchial secretions. Subsequently, secondary bronchial infection occurs, especially by the staphylococcal and pseudomonas organisms. Thus far no immunologic deficiency has been demonstrated to exist in these patients. Pulmonary function tests results will vary with the degree of pulmonary dysfunction; however, the majority of patients who demonstrate evidence of obstructive pulmonary disease will subsequently develop hypoxemia resulting from ventilation to perfusion ratio abnormalities.

Increased production of bronchial mucus and an inability to clear the airways of secretions are critical pathological factors in many common diseases of the lungs (such as chronic bronchitis, cystic fibrosis, asthma, acute respiratory distress syndrome and infectious pneumonitis). Effective treatment of these diseases requires an ability to control the viscosity, rate of production and methods of elimination of mucus.

There is very little information at present on these factors. Further work on the chemistry and pharmacology of mucus production in disease is essential for dealing with these crucial aspects of the pathogenesis of lung diseases. In order to understand the basis of pathogenetic mechanisms involving bronchial clearance in disease, studies of bronchial mucus, chemical structure and physical characteristics will have to be related to the mucociliary clearance functions of the tracheobronchial tree.

Bronchial secretions consist almost entirely of water which is so organized in structure that it does not flow freely through the gel. The organization of water in the gel structure of bronchial secretions is one of the important factors affecting the consistency of secretions. Therefore, more information is required on how chemical agents may change sputum consistency by altering the hydrogen bonding of the water incorporated in the gel. Present information indicates that the gel-structure of bronchial secretions includes a basic protein and two types of glycoprotein which are cross-linked to one another by disulfide bonds. The disulfide bonds can be disrupted by sulfhydryl agents such as N-acetylcysteine or dithiothreitol which in turn also alters the consistency of secretions. However, there is no information on (1) where the disulfide cross-link takes place, (2) whether it occurs before or after secretion, and (3) by what chemical process it is effected.

Similarly, little is known of the factors which control elasticity and viscosity of secretions, factors which are not mutually dependent and can be influenced separately. Of particular relevance is the effect of purulence on the physical properties of sputum and the effect of atmospheric pollutants, such as tobacco smoke, on the production and chemical composition of bronchial secretions. Information is also needed on the specific glycoproteins which provide a skeletal framework for the gels of bronchial secretions.

An understanding of the pathogenesis of cystic fibrosis is essential for the successful diagnosis, treatment and prevention of this disease. Fundamental to such an understanding



is elucidation of the lung defense mechanisms, especially studies of the role of the alveolar macrophage and the immunologic defenses of the lung against infections.

Numerous modes of therapy have been utilized to control the pulmonary infection including antibiotics, aerosols, mist tent, postural drainage, expectorants and mycolytic agents. The effect of this combined therapy appears to be an improvement in the prognosis of this disease as today 60 percent of the patients survive to be at least 10 years of age. The improved life expectancy is felt to be secondary to the comprehensive therapy programs; however, it must be recognized that the improved prognosis is facilitated by the earlier recognition of patients with milder forms of this disease. Controversy exists concerning the role of mist tent therapy, especially in regard to the limited deposition of particles in the lower respiratory tract.

2.12.4 Recommendations

The primary need related to this disease is the identification of the basic biochemical and genetic defects so that biochemical and genetic markers can be developed. This will require the development of accurate methods of detection and biochemical or immunochemical identification of the factors found in biological fluids and tissues from patients with cystic fibrosis. One of the first steps in this program will be the development of a standardized, uniform assay of ciliary motility factor with subsequent employment of more specific and simplified assay techniques. Subsequent studies must be made to discover the origin, mode of action, and relationship of the factor to the molecular defect of cystic fibrosis.



A preliminary report speculating that abnormal methionine metabolism represents a phenomenon basic to cystic fibrosis must be confirmed and expanded. The possible relationship of undermethylated RNA in fibroblasts must be correlated with metachromasia and secretion of factors by fibroblasts.

The comprehensive pulmonary therapy utilized in the treatment of patients with cystic fibrosis must be evaluated to improve (1) the prognosis in this disease and (2) the subsequent rehabilitation of the patient and family.

Although it has not been proven, environmental factors are generally harmful to the lungs of patients with cystic fibrosis. No definite studies of this relationship have been performed and thus epidemiologic studies of the course of cystic fibrosis are needed in patients in different climates, of varying socioeconomic levels, with varying degrees of air pollution and during specific viral infections. Studies of the interrelationship of the biochemical, humoral, immunologic, tissue, viral and bacteriologic factors in regard to the pathogenesis of the pulmonary lesions in these patients are needed.

The evaluation of various rehabilitation regimens and the development of models of comprehensive rehabilitation programs are covered in Problem Area 2, Environmental Respiratory Diseases.

2.12.5 Summary

Cystic fibrosis is one of the main causes of chronic illness in children and young adults and accounts for most of the



deaths in pediatric patients with chronic pulmonary disease. The incidence of the disease in the United States is one in 2,000 live births; thus, 5 percent of the general population in America must be carriers for the gene.

The identification of the basic defect in cystic fibrosis with subsequent successful manipulation and correction of the defect would allow for direct therapy thus improving the prognosis of the disease and decreasing the cost of delivery of care to this group of patients. Improving existing pulmonary therapy programs for patients with cystic fibrosis will result in improved care for all patients with pulmonary diseases. In view of the recent advances in molecular biology, it is quite likely that the basic defect in this disease can be identified.



2.13 ACUTE AND CHRONIC RESPIRATORY FAILURE

This Problem Area is concerned with acute respiratory failure, including respiratory distress syndromes (RDS) as well as acute failure resulting from chronic pulmonary diseases, and with chronic respiratory failure. RDS of the newborn (hyaline membrane disease) is covered separately in Problem Area 11, Hyaline Membrane Disease of the Newborn. Chronic respiratory failure is discussed mainly in terms of problems of therapy and chronic lung diseases are covered in Problem Area 3, Emphysema and Chronic Bronchitis, Problem Area 4, Pediatric Obstructive Respiratory Diseases, and Problem Area 6, Diffuse Interstitial Respiratory Diseases.

2.13.1 Introduction

The sudden onset of respiratory symptoms and signs of severe hypoxemia with or without hypercapnia is defined as acute respiratory failure. Chronic respiratory failure is the presence of chronic respiratory symptoms with or without severe abnormalities of gas exchange.

The concept of acute respiratory distress as a syndrome or group of related syndromes is relatively recent, although the various illnesses or incidents that precipitate the syndromes have been known for a number of years. Although what constitutes respiratory distress syndromes is usually clear to investigators and clinicians working in the field, its meaning is unclear to the great majority of physicians. The syndrome may be generally defined as acute respiratory failure and distress associated with a specific incident or



illness. The respiratory distress syndromes frequently occur in patients with normal lungs and thus are somewhat different from patients with respiratory failure secondary to chronic lung disease. While the approaches to acute and chronic respiratory failure have similarities, for the purposes of this report, RDS is discussed separately from acute respiratory failure as a complication of chronic lung disease.

Conditions listed below, when associated with acute respiratory failure, are included under RDS.

- Traumatic Wet Lung (also, Shock Lung)
- Fat Embolism
- Post Perfusion Lung
- Disseminated Intravascular Coagulation
- Aspiration Pneumonia
- Viral Pneumonia
- Septicemia
- Acute Renal Failure
- Burns
- Smoke or Gas Inhalation
- Drug Overdose
- Immunosuppression
- Oxygen Toxicity
- Long-Chain Hydrocarbon Ingestion
- Radiation Pneumonia
- Neurogenic Pulmonary Edema
- Fluid Overload.

Radiologic and physiologic findings are fairly well delineated as a consequence of considerable clinical investigation. While not all physiologic derangements occur in patients to the same degree, the general pattern is characteristic. Pathologic findings are more difficult to categorize because, in general, pathologists do not recognize RDS, and also because the condition of the lungs at autopsy depends upon whether or not the patient has had therapy. Ultrastructural changes associated with RDS in humans have not yet been studied, except in isolated instances.

2.13.2 Magnitude of Problem

For several reasons, valid statistical data to document the magnitude of the health problem due to respiratory distress syndromes are virtually unobtainable.

- Respiratory distress syndromes have only recently been recognized as such, and their definition has not yet been widely accepted.
- Diagnosis and treatment of RDS depends primarily upon well-trained physicians in the community who can diagnose and treat patients properly. Relatively few hospitals outside of major medical centers have physicians who are specifically trained in acute respiratory care.
- Respiratory distress syndromes are not included in current disease code classifications.

Data from private hospitals representing over 4,650 beds have been obtained. During a one-year period, 3,200 patients were seen with acute respiratory failure and roughly half of these were classified as RDS. Among the group of patients with RDS, there were 400 deaths; a mortality rate of



25 percent. Since these figures were collected from hospitals with intensive care units which were staffed by physicians well trained in respiratory care, the data probably represent optimum care by present standards.

A conservative estimate of RDS in adults is 150,000 cases a year with an average mortality rate of 40 percent. In well-equipped, well-staffed hospitals, the cost of care is about \$5,000 per patient. In assessing the impact of adult RDS as a national health problem, it should be stressed that the syndromes primarily affect young persons who are in their prime productive years; this presents a staggering economic loss to the nation. And in this context, it should also be emphasized that RDS plays an important role in the morbidity and mortality resulting from severe accidental injury.

For acute respiratory failure as a complication in the course of chronic lung disease, the problem of obtaining reliable data on prevalence, morbidity and mortality is equally great. However, some indications can be obtained from studies of survival of very ill patients with chronic obstructive pulmonary disease: treated in an intensive care unit, 65 percent of such patients survive. Data on the survival rate in general wards of hospitals are not available for comparison, but it seems reasonable to assume that survival would be considerably less. Data on survival after discharge are also virtually nonexistent: one study shows that 36 percent of patients were alive one year after discharge from a respiratory intensive care unit.

Reliable data on the prevalence of chronic respiratory failure are similarly unavailable. Estimates of the number of



patients in this country with chronic respiratory disease, based on information from the insurance industry, the Veterans Administration, and the National Institutes of Health, range from 3 to 14 million. A survey of a number of chest physicians in this country and Canada (half in university-affiliated and half in community facilities) revealed that hospital admissions for treatment of chronic pulmonary disease ranged from 1 to 20 percent of all admissions. Estimates of chronic disability attributable to pulmonary disease ranged from 15 to 18 percent.

Neither the crude data on hospital admissions nor the mortality data provide an adequate measure of the health care problem or the economic impact of chronic respiratory disease; chronic obstructive pulmonary disease is probably considerably underdiagnosed. Hospital admissions represent only those patients most severely affected. The disability of these patients for many of their most productive years and the many hospitalizations required during exacerbations are not reflected in these data.

2.13.3 Current State of Knowledge

Diagnosis

The last decade has seen a broadening approach to acute respiratory failure. Major advances have been made in the techniques of diagnosis and care for acute respiratory insufficiency in hospital, and recommendations have recently become available on the essentials of an intensive respiratory care unit and on the organization and staffing of intensive care units.



The early recognition of respiratory failure and of acid-base disturbances has been greatly facilitated by the widespread use of blood gas electrodes. In some cases, the device may have preceded and actually encouraged reeducation of physicians. It is likely that increased use of blood gas analysis has resulted in earlier diagnosis of hypoxemia.

To a great extent, recognition of respiratory distress syndromes depends upon the astuteness and knowledge of the attending physician or nursing personnel. A lack of physicians trained in pulmonary or respiratory care, combined with inadequate care facilities and personnel in many community hospitals, hampers both recognition and treatment of RDS and almost certainly contributes to a higher than necessary mortality. At present, the best clinically available technique for early detection is serial monitoring of arterial blood gases in high-risk patients.

Diagnostic tests which would lead to earlier detection and treatment would help greatly to reduce morbidity. Since the earliest pathologic manifestation of acute pulmonary injury appears to be accumulation of interstitial edema fluid and protein, a method which could detect early increases in lung water would be highly desirable. Ideally, this method should be noninvasive, simple to perform, of low risk to the patient, reliable, repeatable, sensitive and relatively inexpensive.

Current approaches to this problem include radioactive tracer studies, thermodilution techniques, and transthoracic electrical impedance. All of these current investigative approaches have serious limitations. Microelectrodes for

continuous monitoring of arterial PO_2 are at present too expensive and fragile for routine use and are invasive and do not discriminate edema formation from other causes of hypoxemia. While changes in functional residual capacities and in physiological dead space are found in advanced RDS, it seems unlikely that these measurements would be sensitive or specific enough to detect early edema formation.

Research in the area of recognition of RDS should be directed to the development of ideal detection and monitoring.

Pathogenesis of RDS

With the exceptions of aspiration pneumonia, direct trauma to the lung and possibly fat embolism, little is known of the mechanisms of lung injury. Surfactant loss has been noted in adults with RDS, but it is not clear whether this is a cause or result of RDS. Despite much study, the biochemistry of surfactant, its site of production, and its location in relation to the cell membrane are still areas of controversy. There is no simple biochemical test for its presence, absence, or degree of activity. Although the alveolar capillary membranes seem to be the prime target sites for injury, practically nothing is known about membrane physiology or biochemistry of the normal or injured lung.

The role of genetic or immunologic factors which might protect or predispose to RDS are completely unknown. At present, both approaches appear unpromising except as they relate to subsequent sepsis, which is discussed below.

The role of vasoactive substances in RDS is incompletely understood. Platelet aggregation, intravascular coagulation, fat embolism, air embolism, amniotic fluid embolism and marrow embolism have all been demonstrated as causes of RDS. The mechanisms associated with multiple emboli and acute hemorrhagic edema are unclear. In fat embolism, the release of free fatty acids has been postulated, but has not been proven conclusively.

Pathologic studies of RDS at the electron microscopic level are few in number and are open to criticism, since most are post-mortem. It is unlikely that the pathologic development of RDS will be understood in humans unless a safe sequential biopsy technique can be developed. The use of high-speed pneumatic drills offers some promise in this area, but the risk to the patient is considerable. The benefits in terms of understanding of disease from both a biochemical and pathological standpoint might be enormous if more were known about the reaction of the human lung to injury. Similar studies need to be performed in animal models, but the primary need is human pathology.

Some patients with RDS survive the initial insult but then develop pulmonary fibrosis. The mechanism of this is not understood, but its intensive study could yield clues to the entire field of interstitial fibrosis. While oxygen has been blamed as the cause of interstitial fibrosis in these patients, this has not been proven, and it seems likely from clinical observations that infection may play a significant role although at present they are entirely unknown.

The natural history of patients with RDS needs better delineation through long-term studies. While most patients that recover seem entirely well, reports on follow-up of these patients are scanty. It would seem important to obtain documentation on those patients who recover without permanent injury and those that are left with residual lung damage. A study of genetic and immunologic differences between these groups could yield important information.

Therapy: Acute Failure and RDS

Current therapy has concentrated on correction of ventilatory derangements and hypoxemia. The techniques used (volume respirator, large tidal volume, positive end-expiratory pressure and careful attention to inspired oxygen concentration) are based on physiologic derangements that are now relatively well understood. Little more is likely to be gained by stressing the physiologic approach in investigation of RDS. This therapy is primarily valuable in preventing death from acute hypoxemia. As such, it has undoubtedly saved the lives of many patients whose underlying injury was self-limited or controlled by other therapeutic measures.

Pharmacologic approaches to correction of the underlying injury have consisted in attempts to remove water from the interstitial space of the lung, in the use of corticosteroids, and in the use of antibiotics to prevent infection. The use of salt-poor albumin combined with potent diuretics has much promise and has been studied in both animals and humans. Human studies, however, have not been controlled or extensive enough to prove the value of this method.



Corticosteroids have been used with success in the treatment of fat embolism, but experimental evidence is lacking and the method of action is only conjectural. In addition, controlled clinical trials have not been done. In aspiration pneumonia, animal experimentation has indicated that corticosteroids are useful and they appear to be useful in patients as well, but controlled studies are lacking. The use of corticosteroids in shock has been advocated on the basis of experimental evidence, but its value in patients is still unproven. The extreme difficulty in conceiving and executing controlled studies that involve critically ill patients with multiple problems will probably continue to act as a barrier to these studies and other pharmacologic studies in such patients. While pulmonary vasodilators have been used in infantile RDS they have not been of particular value. They have not been evaluated in adults with RDS. It seems likely that new pharmacologic approaches will come only when there is a better understanding of the underlying mechanisms of injury.

Membrane oxygenators have undergone considerable investigation as a therapeutic method of sustaining life in RDS. While the early results were disappointing, recently successful outcomes have been reported after prolonged use of membrane oxygenators. This technique is very expensive in terms of personnel, equipment, and backup facilities, but it has reached a state of maturity that now requires limited, clinical assessment of its efficacy.

In regard to acute respiratory failure in the presence of chronic lung diseases, the principles of management of alveolar hypoventilation and associated problems are now



also well established. However, despite this encouraging aspect, it is apparent that advances in knowledge and their application to therapy have not been disseminated adequately to the more isolated or rural areas. In addition, even in enlightened centers, the increasing use of blood gas analysis and artificial ventilation has resulted in a mechanistic approach to the problem, while underlying endobronchial infection, bronchoconstriction, and fluid retention may go untreated. Examples of problems warranting further study are discussed below.

Infection continues to play a major role in the morbidity and mortality associated with acute respiratory failure. In addition to causing acute respiratory failure in patients with chronic lung disease, pulmonary infections can cause severe respiratory failure in previously healthy individuals; e.g., influenzal pneumonia, with or without superimposed staphylococcal pneumonia. Respiratory failure due to pneumonia carries one of the highest mortality rates of the patients in respiratory care units.

Studies are needed to determine factors that influence individual susceptibility to primary and secondary infection; for example, host defenses, interactions with other disease entities, macrophage inhibition, and the interaction of various antibiotics. In addition, methods should be developed to control secondary infection within a respiratory care area due to: airborne contamination, transmission from patient-to-patient, from personnel-to-patient, and from use of suction catheters and inhalation therapy equipment.



Cardiac disturbances should be studied to elucidate the mechanisms responsible for the apparent propensity toward cardiac arrhythmias in patients with acute respiratory failure. Such investigations should determine the precise nature of these arrhythmias and their relationship to the clinical conditions, the drugs which have been administered, and the status of acid-base and electrolyte balance, gas exchange, or other factors.

Burn injury needs investigation, as little is known about the effects of combustion products of newer synthetic materials on the tracheobronchial tree and lungs. The effects of common household combustion products should be studied in animals. The healing process should be documented so that guidelines for therapy in severely burned humans can be developed, particularly with regard to the role of infection and antibiotics, steroids, and cardio-pulmonary bypass.

Aspiration pneumonia should be studied to determine precisely the type of injury produced by aspiration. Most studies of aspiration relating to pH, use of steroids, antihistamines and other factors have been done in a casual way and much remains to be answered. The reason for persistence of pulmonary abnormalities and respiratory failure in some patients, while others are left with little or no chronic pathology, is still unknown.

Oxygen toxicity is difficult to define in terms of morbidity and mortality because many patients undergoing oxygen therapy have also received a number of drugs or have been exposed to therapeutic devices. The need for oxygen therapy in acute



hypoxemia is well recognized. Different modes of administration have been evaluated and several techniques for the administration of low concentrations of oxygen advocated. But when patients have received high concentrations of oxygen for a number of days, the relation between the final pathologic picture and initial acute respiratory disorder is difficult to determine. It is possible that an animal model could be developed in which oxygen toxicity would be specifically produced, and the short- and long-term pathologic changes documented.

Respiratory monitoring is still in its infancy. Many physiologic and mechanical complexities are involved. The commonest cause of sudden death in patients on ventilators is mechanical obstruction or simply disconnection. The best respiratory monitor available today is a nurse at the bedside. As a consequence of inadequate staffing, inadequate facilities, and improper attitudes, many patients are left alone on ventilators, without proper attention or monitoring facilities.

Measurement of blood gas tensions, respiratory rate, tidal volume, and peak pressure on ventilators are extremely valuable in detecting changes in lung function, and yet these simple techniques frequently are not used.

Spirometer alarms and low pressure alarms provide a simple and reliable way of monitoring for the common disasters, but they are seldom specified in criteria for intensive care units and are used infrequently in many hospitals.

Follow-up care of patients who have had an acute exacerbation of respiratory failure is being increasingly emphasized in order to prevent readmissions to the hospital. Experience in several centers suggests that a home care program, actively pursued, can keep the patient with respiratory failure out of the hospital. Wider experience with these programs is needed in order to assess their effect on mortality, morbidity, and the economics of health care.

As some patients seem destined to spend their remaining lives on ventilators, support and encouragement for the development of chronic respiratory care centers for this group of patients should also be considered.

Therapy: Chronic Failure

As chronic respiratory failure is most common in patients with chronic obstructive pulmonary disease (COPD), this condition is used as a model for much of this section.

Because of the scarcity of research in the therapy of chronic respiratory failure, it is difficult to find careful, well-formulated investigations that clearly demonstrate the efficacy of various approaches to patient care. Unless specific infectious agents, or an immunologic or biochemical reaction, can be implicated, treatment of both acute and chronic respiratory failure is directed at physiologic abnormalities, and the principles of management of these two conditions are similar. Most treatment is of transient benefit. There is no clearly documented evidence of its value in terms of disease progression, mortality reduction,

or other factors that are important in the patient's ability to lead a useful existence. The current state of knowledge with regard to commonly used modes of therapy is briefly commented upon below.

Corticosteroids are the non-specific treatment of choice in severe asthma which is not relieved by conservative therapy, in allergic interstitial pneumonitis, and in some collagen diseases and granulomatoses in which there are immunologic determinants. The role of steroids in COPD is still in question since there are few, if any, well-controlled studies. Steroids have been shown to be effective in some patients but not in others. In general, they are believed to be of value only when there is bronchoconstriction that does not respond to usual bronchodilator therapy, and they are thought to be of no value in patient emphysema. Except for the occasional young patient with extrinsic asthma, the efficacy of hyposensitization therapy in asthma has not been satisfactorily demonstrated.

Bronchodilator therapy appears to be of transient value according to studies in which bronchoconstriction was documented by clinical or physiologic methods. Its value in emphysema in the absence of bronchoconstriction has not been demonstrated. However, it may be of some prophylactic value in preventing airway obstruction caused by non-specific irritants. While additional studies on the effectiveness of bronchodilators are not likely to add much of value, there is a need for investigations on the best procedures for administering them. In addition, carefully controlled studies of the overall long-term role of bronchodilators are needed.



Treatment of heart failure in chronic respiratory insufficiency is controversial, although most physicians concede that digitalis and diuretics are of value when cardiac failure complicates chronic lung disease.

Treatment of infections with the appropriate antibiotic should be used when acute infection develops in patients with chronic respiratory disease. Antibiotics used prophylactically do not prevent recurrent infections but do lessen their severity. Empiric (broad-spectrum) antibiotic therapy may be clinically acceptable in management of chronic respiratory insufficiency when exacerbation of symptoms seems to be due to infection, but this has not been unequivocally established. Although gram negative bacilli are commonly demonstrated in the sputum of patients with COPD, their role in the genesis and perpetuation of chronic bronchitis is unknown. Moreover, the role of viral infections has not been clearly identified.

Thinning of secretions with mucolytic aerosols may be of benefit when used intensively for short-term therapy, but for long-term use its clinical superiority over hydration by systemic and aerosol routes has not been demonstrated. Humidifying aerosols appear to be less effective than systemic hydration; there is no evidence that the chemical agents or enzymatic agents are superior. The clinical efficacy of expectorants or cough suppressants in chronic respiratory insufficiency has not been well studied.

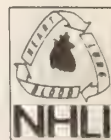
Physical therapy in the management of patients with chronic respiratory disease is controversial. Theoretically, retraining in obstructive lung disease with slow and deep



breathing should reduce the work of breathing. Some studies have demonstrated that by slowing respiration the oxygen-cost of breathing is decreased, but others show more efficient oxygen extraction at rest and some slight improvement in ventilation-perfusion relationships. In general, physical therapy seems to have a positive effect on patients in that they report improvement in symptoms, but these effects might be related to the psychological benefits of increased activity. There are no properly controlled studies of the long-term effects of breathing retraining.

Postural drainage and pummeling increased the evacuation of sputum and reduces bronchial obstruction in acute respiratory infections or when bronchial secretions are retained. But specific benefits of postural drainage have not been documented for patients with CCPD, except for its beneficial effects in localized airway disease (bronchiectasis).

Exercise training in patients with chronic airways obstruction has essentially the same physiologic effects as physical training in normal subjects. Investigations have shown that a program of daily graded exercises, sometimes with the necessary support of supplemental oxygen, results in an improved sense of well-being and often a significant increase in exercise tolerance. The improved capacity for exercise is accompanied by a reduction in cardiac rate and, if breathing retraining has been instituted, in a slowing of respiratory rate. But there is no improvement in respiratory function and the increased exercise tolerance may not carry over to other activities. The application of graded increases in activity to occupational or household chores (i.e., occupational therapy) has been virtually ignored. While there is



no question that for some patients existence is improved considerably, there are no properly controlled studies which demonstrate that physical conditioning alters the course of the disease, morbidity, or mortality rate. The effects of physical conditioning in patients with chronic respiratory disease are difficult to distinguish from the effects of improved efficiency of performance of a given task, increased motivation, and lessened psychological stress. Documentation is needed to demonstrate whether physical conditioning has additional benefits.

Oxygen therapy is necessary in acute hypoxemia but its role in chronic situations is controversial. Certain patients with chronic airway obstruction may benefit significantly from supplemental oxygen therapy, particularly during exertion, but the studies demonstrating its benefit in improving a patient's exercise tolerance have been carried out primarily at an altitude of 5000 feet. The role of continuous ambulant oxygen therapy should be evaluated at sea level, and there should be continued research into the role and long-term effects of oxygen administration in both acute and chronic respiratory failure.

Removal of irritants from the patient's environment is essential. The association between cigarette smoking and development of COPD has been well established and there is evidence that disability and absence from work is greater in bronchitics who continue to smoke. Although there is no evidence that progression of pathologic or physiologic abnormalities is retarded in patients with advanced disease, cough and sputum production are reduced or eliminated by cessation of smoking. Moreover, it has been demonstrated



that dysfunction of small airways in asymptomatic smokers is reversible if smoking is discontinued. All therapeutic measures directed at COPD are overshadowed by comparison with the effect that a moratorium on smoking or the development of the "safe" cigarette would have on this problem.

Publications aimed at altering the habits of the public, although produced by professional bodies, have had little impact. Clinics for volunteer individuals have had significant failure rates. Stepwise increases in taxation of tobacco products have had only temporary effect in reducing overall consumption. Efforts should be directed toward identifying the psychological and pharmacologic factors leading to dependence on smoking, the most effective techniques for breaking this dependence, and the development of the safe cigarette.

Comprehensive long-term treatment programs doubtless prevent some early deaths from chronic respiratory disease and often allow the patient to function more effectively despite persisting disease. Home-care programs, in which there is continuous supervision by medical and paramedical personnel, can result in significant reduction in hospital admissions and hospital days. However, it seems that function continues to deteriorate slowly with little, if any, effect on the excessive mortality rate. The few available assessments of comprehensive in-hospital and ambulatory care programs (which do seem to produce some initial subjective and objective improvement) have revealed disappointing results when viewed in terms of survival or alteration of progression of the disease.

To assess adequately the effectiveness of coordinated home-care services, models should include some of the following components: physicians' assistants, physiotherapy, home help, oxygen, nurses, social services and "meals-on-wheels." Moreover, it is essential in such studies that the patient conditions be comparable and that the endpoints of therapy be specified and measured. Endpoints should include prolongation of life, improved activities or daily living, and increased life satisfaction.

Available Resources

Data on physical and professional resources for chronic respiratory care are scarce. Although there have been a few surveys of hospital resources, most of them have been conducted in areas where a state thoracic society was active and these probably reflect better-than-average resources.

The majority of these surveys emphasize services and equipment but omit information on medical supervision and direction. The available information does not include the facilities and personnel for management of chronic respiratory insufficiency, a condition which in many respects is more demanding and challenging than acute respiratory failure.

Facilities such as hospital beds, pulmonary laboratories, pulmonary therapy facilities or equipment for respiratory care range from excellent to almost nonexistent. In part, their differences depend upon the availability of professional manpower, but in some instances the equipment and facilities have actually preceded the manpower.



There are no national standards for resources for care of patients with acute and chronic respiratory insufficiency. These should be developed and included in hospitalization accreditation requirements. Many hospitals still attempt to manage patients with acute respiratory failure without proper facilities or staff.

Facilities for comprehensive care and emergency services should be available to the patient with chronic respiratory insufficiency in each medical community, the depth and specialization depending upon the size and resources of the community. Massive programs for rehabilitation of patients with advanced respiratory insufficiency are probably not warranted at this time, but long-term care with supporting services, which would include home care and rehabilitation, could be provided by properly utilizing existing agencies and facilities.

Evaluation and Development of Community Emergency Services

Accessible and effective community emergency services are of vital importance in the treatment of respiratory disease emergencies. Present emergency facilities (emergency rooms, respiratory care units, etc.) should be evaluated in terms of their accessibility and efficacy in handling respiratory disease emergencies. Present standards of medical emergency practice should be evaluated. Also, emergency care practitioners including physicians and allied health professionals should be evaluated in terms of their ability to effectively utilize both present facilities and up-to-date medical emergency practices.



In conjunction with the gathering of this important data, planning and research should be begun in order to develop an effective model of an emergency facility which is able to deal with respiratory disease emergencies. Areas of high population density, outlying communities and emergency vehicles should be considered in the overall question of accessibility. Advances in communication systems for emergency vehicles and outlying communities, new cadres of allied health professionals (emergency care physician assistants) and the application of bioengineering technology toward the development of emergency respiratory care equipment will also play an important role.

Finally, these models should be established in varying geographical locations and with varying components such as staffing, technological resources, and standards of emergency respiratory disease practice in order to identify the most effective models. Then, these models can be utilized for different areas of the country, where appropriate, according to needs and resources available.

2.13.4 Recommendations

Prevention requires determination of the natural history of RDS and acute and chronic respiratory diseases, long-term assessment of postrespiratory failure, coding systems for respiratory distress syndromes, longitudinal studies of patients with chronic respiratory diseases, and studies of the mechanism of lung injury.

Detection and diagnosis will require more careful assessment of patients with long-term disease with methods for earlier detection of respiratory distress syndromes.

Treatment and management will require controlled clinical studies of various treatment modalities including corticosteroids, bronchodilators and other pharmacologic compounds, digitalis and diuretics, physical therapy, exercise training, oxygen therapy, removal of irritants, mechanical ventilators, membrane oxygenators, and development of new modalities of treatment and management. Also of key importance will be the establishment of model community emergency care centers to test various therapeutic modalities as well as to develop standards for organizational and training support.

Repair mechanisms of the lung should be studied. Long-term assessment of patients who have recovered should be pursued, and those factors that might help to identify individuals with a greater chance of recovery should be identified. Finally, basic reparative processes, including collagen and other connective tissue metabolism and alterations in morphology and function of lung cells, should be studied. The evaluation of various rehabilitative regimens and the development of models of comprehensive rehabilitation programs is covered in Problem Area 2, Environmental Respiratory Diseases.

2.13.5 Summary

Acute and chronic respiratory failure and adult respiratory distress syndromes account for a very significant amount of morbidity and mortality in this country. Adult respiratory distress syndromes have only recently been described. Conservative estimates of incidence are approximately 150,000 cases a year with 40 percent mortality. It is important to note that primarily young people in their productive years

are affected. Approximately 3 to 14 million Americans are affected by chronic respiratory disease. Estimates of chronic disability attributable to pulmonary disease range from 15 to 18 percent. Research is needed in order to define better the adult respiratory distress syndromes and to investigate etiology and pathophysiology so as to develop effective preventive measures. Epidemiologic studies and animal models will be of much value. Detection, especially in early adult respiratory distress syndromes, will play an important role in decreasing morbidity and mortality. New techniques and devices need to be developed through the application of advance bioengineering technology. Treatment should be thoroughly evaluated by controlled clinical trials and new modalities should be investigated. Community emergency care centers should be established to serve as a focus for therapeutic efforts.



2.14 EXTRAPULMONARY MANIFESTATIONS OF RESPIRATORY DISEASES

2.14.1 Introduction

Patients with respiratory disease commonly demonstrate extra-pulmonary manifestations of their disease. These stem largely from abnormal pulmonary gas exchange resulting in hypoxemia, hypercapnia and acidosis (HHA). In turn, these produce abnormal function of many organs and cells.

2.14.2 Magnitude of Problem

It is not possible to estimate the number of patients with these disorders. Control of them would alleviate much of the disability associated with respiratory disease.

2.14.3 Current State of Knowledge

Recent studies have focused upon the importance of the lung as a metabolic organ. The lung participates in a number of metabolic transformations in which a variety of chemical agents are synthesized, stored, modified, inhibited, or degraded. (A partial list of these is shown in Table 2.1.)

At this time, the changes in these transformations produced by various lung diseases are not well delineated. Nor are the changes in cell and organ function secondary to changes in lung metabolism well understood. In the near future, major advances in understanding should occur and provide important pathogenetic, diagnostic and therapeutic advances.

Table 2-1
METABOLIC FUNCTIONS OF THE LUNG

Role Of Lung In Metabolic Transformation	Local (Pulmonary) Effects	Systemic (Extrapulmonary) Effects
1. Biosynthesis a. Normal Lung Cells Secretory Antibodies Prostaglandins Kallikreins Histamine Interferon Proteolytic Enzymes Proteolytic Enzyme Inhibitors Slow Reaction Substance of Anaphylaxis (SRS-A) Surfactant	IgA in Bronchial Secretions, Local Varied - e.g., Bronchodilatation by Prostaglandin E Pulmonary Hypertension, Alveolar Duct Constriction Bronchial Smooth Muscle Constriction, Increased Vascular Permeability Anti-Viral Breakdown of Proteins, Tissue Destruction Protection of Tissue From Proteolytic Injury Bronchial Smooth Constriction, Increased Vascular Permeability Surface Tensions Lowering Effects in Alveoli - Stabilizes Alveolar Size	Spill Over into Circulation Leading to Altered Immunologic Status Varied - e.g., Diverse Cardiovascular Effects Such as Tardycardia, Vasodilatation, Facilitate Adrenergic Transmission to Vascular Smooth Muscle Systemic Hypotension, Increased Vascular Permeability Increased Vascular Permeability Anti-Viral Breakdown of Proteins, Tissue Destruction
b. Lung Tumor Cells Acth-Like Peptides ADH-Like Peptides Parathormonoid Peptides Insulinoid Peptides Gonadotropinoid Peptides Thyrotropinoid Peptides Serotonin (+ Kinins) Nervous System Antimetabolism Growth Hormone Multiple Polypeptides	Pulmonary Vasoconstriction Bronchial Constriction	Cushings Syndrome Water Retention and Hypoanremia Hypercalcemia Hypoglycemia Gynecomastia Hyperthyroidism Carcinoid Syndrome (See Kinins) Peripheral Neuropathy, Cerebellar Degeneration, Cerebral Degeneration, Eaton-Lambert (Myasthenic Syndrome) Osteoarthropathy and Acromegaly Multiple Syndromes
2. Conversion and Activation Angiotension I to Angiotension II Via Converting Enzyme Bradykinins	See Kallikreins	Vasoconstriction Aldosterone Release See Kallikreins
3. Removal (Binding, Inactivation, Degradation) Bradykinin Serotonin Prostaglandins E and F Histamine Norepinephrine	See Kallikreins See Above See Above See Above	See Kallikreins See Above See Above See Above Adrenergic Stimulation

The lung serves as a portal for a wide variety of chemical agents which then may injure extrapulmonary structures. The approaches to this class of respiratory disease are emphasized in Problem Area 2, Environmental Respiratory Disease.

2.14.4 Recommendations

Prevention will require studies on organ effects of hypoxia, hypercapnia, and acidosis (HHA). Although major emphasis in the specific proposals are given to the effects of HHA on the brain, these are intended only as a model. Similar studies involving the effects of HHA on liver, heart, kidneys, muscle, and indeed on the lung itself, are required.

Investigation into the brain effects of hypoxia, hypercapnia and acidosis should include adverse effects of ventilatory therapy in lung diseases on cerebral circulation, metabolism and function, adjustments of cerebral circulation to abnormal blood gases, mechanism of brain dysfunction during hypoxia, mechanism and treatment of brain edema in chronic lung disease, mechanism and prevention of CO₂ narcosis produced by oxygen therapy, pharmacologic agents used in lung disease, brain ECF acid-base balance and its alteration by lung disease, and contribution of chronic lung disease to the brain dysfunction of the aged.

Laboratory studies on the influence of hypoxia, hypercapnia and acidosis on growth and development of the newborn should include studies on placental function, placental development, enzymatic and cellular changes in the fetus, adaptive changes



in acute and chronic exposures to hypoxia, hypercapnia and acidosis, and the role of hypoxia, hypercapnia and acidosis in the genesis of abnormalities such as hyaline membrane disease.

Controlled prospective epidemiologic studies should be conducted on selected populations. These should help to identify fetal wastage incidence of fetal abnormalities, neonatal mortality, growth and development over early years of life, and adaptive changes which permit long-term residents at high altitudes to produce viable offspring.

Investigation into cellular, biochemical abnormalities produced by hypoxia, hypercapnia and acidosis should include the improvement of techniques for in vivo and in vitro determinations, evaluations of morphological and membrane alterations, changes in steady state fluxes in response to low oxygen tension, assessment of intracellular milieu in acute and chronic alterations, determination of abnormal levels of cellular constituents, causes of cell death and degeneration, biochemical relations in cellular adaptation, primary versus second order effects, effectiveness of pharmacologic agents on cellular metabolism, patterns of enzyme adaptation in response to hypoxia, hypercapnia and acidosis, cellular ionic regulation, and effects on metabolism of changes in intracellular and extracellular pH.

Studies on humoral agents should be conducted in reference to the lung as an organ which synthesizes, degrades, inhibits, and accentuates certain humoral agents. These studies should include investigation into the biosynthesis and release of bioactive agents, metabolism of agents, pharmacologic agents, and biotransformation of exogenous compounds of the lung.



The biochemical aspects of tissue metabolism in high-altitude dwellers should be studied. These studies should include the hematological control during high-altitude adaptation, cellular and metabolic adaptations to high altitudes, vascular adaptation at high altitudes, pharmacologic responses in high-altitude dwellers, genetic factors in response to high-altitude hypoxia, and enzyme adaptation in high-altitude dwellers and cellular chemical changes in response to high altitude.

Also needed are epidemiologic studies on selected patients, identification of the alteration of humoral agents found in the diseased lung, and definition of the biochemical aspects of tissue metabolism in chronically hypoxic humans, such as those found at high altitudes.

Detection and diagnosis requires the development of sensitive techniques for monitoring the early manifestations of HHA.

Treatment and management require new approaches to the therapy of HHA, as well as to the other extrapulmonary manifestations of respiratory disease.

Clinical studies should be conducted concerning the treatment of hypoxia. These studies should include the identification of the changes in pulmonary structure and function produced by high oxygen inhalation, design of instrumentation for monitoring changes in lung function during oxygen inhalation, studies of the effect of high oxygen inhalation on organs in addition to the lung, investigation of potential agents and approaches to reverse pulmonary oxygen lesions,



investigation of potential agents and approaches to reverse oxygen lesions in other than the lung, development of agents and approaches to augment blood oxygen transport during hypoxia, augmentation of enzymatic support of anaerobic glycolysis to improve energy supply during hypoxia, augmentation of enzymatic support of oxidative phosphorylation to improve efficiency of oxygen utilization, development of agents and approaches to reverse abnormal redox states, tailoring of tissue metabolic needs and tissue responses to decrease oxygen supply, and development of nongaseous forms of systemic oxygen administration.

2.14.5 Summary

Extrapulmonary manifestations of respiratory disease are an important by-product of respiratory disease and have not been studied to any great extent. At present, there is much interest in the lung as an organ which both synthesizes, and degrades and inhibits chemical factors. Investigation into the effects of hypoxia, hypercapnia and acidosis on the brain growth and development of the newborn and cellular biochemical abnormalities is needed. Epidemiologic studies on selected populations should be performed, and biochemical aspects of tissue metabolism in high-altitude dwellers is important to study. Finally, the treatment of hypoxia deserves significant attention, and development of new modes of therapy will contribute much to the management of respiratory disease.



2.15 EDUCATION IN LUNG DISEASES

2.15.1 Introduction

Despite the enormormous broadening of knowledge and interest in pulmonary diseases, relatively little attention has been given to the distribution of this knowledge in an effective manner to the various groups who require it.

In the course of implementing an expanded lung program a significant and purposeful educational plan is required in order to fulfill the goals of prevention, detection and diagnosis, treatment and management, and rehabilitation. This should be directed not only at physicians and medical students but to allied health professionals, the public at large, patients themselves and their families.

2.15.2 Recommendations

Manpower

Adequate numbers of scientific personnel are required to implement the scientific and clinical portions of an educational plan as it proceeds. This will require a comprehensive proposal which documents the personnel required to carry out the various portions of the plan. Such a plan will not only involve medically trained scientists, but also basic scientists in the areas of physiology, biochemistry, biophysics, genetics, immunology and epidemiology. Moreover the plan should include the training of allied health professionals such as physician assistants, respiratory-disease nurses, laboratory technicians, and

physical, occupational and inhalation therapists. To develop a plan for educational needs, a committee of outside consultants should be established to estimate the number and kinds of personnel which are required. This committee should have the responsibility of evaluating the effectiveness of educational programs as well as revising the educational plan on a periodic basis as needs change. It would be important to have at least one full-time staff member involved in this activity.

The postgraduate education of physicians should provide such instruction as will maintain high levels of care for patients with lung disease. Programs of this nature should be geared so that the physician's role in community health programs will be insured (see below).

In order to provide an adequate pool of physicians required for the delivery of effective health care in the area of lung disease, a long-term program should be developed for the teaching of lung disease to undergraduate medical students. For this purpose, the teaching of lung disease to undergraduate medical students requires revision and modernization. Careful periodic review will be necessary to prevent either an oversupply of or too few chest physicians for the needs of the country.

General Public

The general public must be made aware of the causes and prevention of lung disease, its early signs and symptoms, the limitations it imposes and methods for the avoidance of environmental irritants with the potential for causing lung damage.



Patients with respiratory disease rarely understand its implications and, in the chronic forms, the restrictions it places upon them. This is no less the case with their families. A structured effort should be made to provide this knowledge.

Educators

Various levels of educators should be trained to provide the necessary instruction. These should include:

- Adequate numbers of medical school and public school teachers of respiratory disease
- Adequate numbers of allied health professional teachers in the lung disease area.

The development of the communication media for public transmission and the addition of new dimensions in public education will also be important.

Professional Education

Programs will obviously vary with the requirements to be met. Those provided for the undergraduate medical student will obviously differ from those required by the practitioner of medicine with no special experience in pulmonary disease. Methods, moreover, will differ significantly when directed to allied health professional personnel or to physicians entering the specialty of lung disease.

In addition to traditional teaching techniques, such mechanisms as audiovisual tapes, closed circuit television,



programmed learning and computer-based case studies may contribute significantly to a clearer appreciation of the problems at issue.

In public education, there is need for recognition of environmental factors that underlie many severe lung conditions and of measures which may be taken to avoid these. Requisite is an understanding of the respiratory process and how disease places limitations upon this. The program may be effected utilizing various levels of medical or allied health professional talent appropriate for the audiences to be instructed.

The patient who suffers from pulmonary impairment should receive instruction in the reasons for his restriction, the evaluative techniques to which he is subjected and the manner in which he may adapt to his limitations. Similar efforts should be made in the case of families of these patients. In preparing for such efforts, there is need for educational talents capable of designing methods of operating and of measuring their applicability and usefulness. These individuals will plan, organize and implement the programs desired and be involved in both surveillance and quality control.



PART III

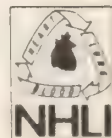
SUMMARY OF PANEL RECOMMENDATIONS



PART III.

SUMMARY OF PANEL RECOMMENDATIONS

This report suggests a multifaceted and balanced approach towards the development of effective measures for the prevention, detection and diagnosis, treatment and management, and rehabilitation of lung diseases. The basic strategy is to move on many fronts rather than to emphasize limited areas; it is felt that this will provide maximal returns in a shorter period of time. In addition, there are important interrelationships among the different respiratory diseases and Problem Areas in this report, interrelationships which require a broad, multifaceted approach rather than a concentrated effort of more restricted scope if rapid progress is to be made. The elements of this approach involve research, development of model clinical programs, and development of model programs aimed at the prevention of lung disease. The proposals involving research have a



number of elements which are common to all the disease areas:

- Basic research which is vital to new insights and understanding
- The development of new animal models and the wider use of existing animal models of disease to accelerate the translation of basic research into a clinically usable form
- Clinical research to determine the specific approaches required in the various respiratory diseases
- Clinical trials to evaluate present and future methods of detection, treatment and rehabilitation
- The wider use of biomedical engineering to provide new technologies aimed at the control and treatment of respiratory diseases
- Epidemiologic studies to determine the incidence and natural life history of the various disease processes as well as to provide leads concerning etiology.

Since these epidemiological studies are needed in virtually all of the disease categories, a unified mechanism centered at the NHLI for conducting these should be developed.

This report describes the development of a number of key clinical programs in emergency care, rehabilitation and education. These programs should be set up as models designed to answer specific clinical questions as efficiently and expeditiously as possible.



Education of both scientific personnel and the general public is considered to be vital to the successful implementation of the suggested program. Therefore, scientific and general education proposals are made in a separate segment of the report.

Rehabilitation applies to most of the diseases covered. Major emphasis is provided in Problem Area 2 (Environmental Respiratory Diseases), but the proposals contained in that section are applicable to most other respiratory diseases covered in this report. In similar fashion, emergency care services are primarily emphasized in Problem Area 13 (Acute and Chronic Respiratory Failure) although the proposals in that section are generally applicable to the other respiratory disorders.

Respiratory diseases of infants and children are specifically considered in Problem Areas 4 (Pediatric Obstructive Respiratory Diseases), 11 (Hyaline Membrane Disease), and 12 (Cystic Fibrosis). In addition, the relationship between respiratory diseases of children and adults is found in the sections on most of the other disease categories.

The following sections summarize recommendations with respect to each of the 15 Problem Areas.

Major emphasis is required on studies of the normal lung for several reasons. Relatively little information is available concerning the cellular biology, cellular physiology and cellular biochemistry of lung cells. Many of the major advances of molecular biology have not been applied to studies of the lung. These studies are critical for any progress in detection and diagnosis, and management and treatment, as well as rehabilitation.

The lung is rich in collagen and elastin. It is clear that many of the most important lung diseases, such as emphysema and interstitial lung disease, involve fundamental abnormalities in connective tissue (collagen and elastin) metabolism. Yet little is known about the normal function and metabolism of these proteins and even less about the alterations that occur with disease.

Basic studies are needed of collagen, basement membrane collagen, elastic fibers and other protein components of the lung. Pertinent problems include:

- The quantities of connective tissue components in normal lungs, and differences in their distribution with age, sex and environmental influences
- The amino acid composition of collagen and elastin in lung tissues, their chemical precursors and their possible variations with age, sex and environmental influence

- Variations in quantity and amino acids composition of connective tissue components of lung in diffuse pulmonary fibrosis and in various types of airway obstructive disease
- Relationships of surface forces of alveoli to the mechanical characteristics of tissue components of the lung
- The kinetics of synthesis of elastin and collagen
- The in vivo balance and interaction among proteolytic enzymes with potential for altering pulmonary connective tissue.

The lung is composed of a vast number of different cell types, and loss and replacement of these play an important role in many different lung diseases. Therefore, measurements of cellular turnover rates of lung cells and the alterations in these rates with disease require further study.

Bronchial mucus is an important factor in the defense mechanisms of the lung. Alterations in bronchial mucus are found in chronic bronchitis, in cystic fibrosis, in various pulmonary infections and in a diverse group of lung diseases. Studies are, therefore, required of the structure, synthesis, physical and physicochemical characteristics of normal bronchial mucus.

Another vital defense mechanism involves ciliary function in the bronchial tree. Investigations of ciliary structure and function are crucial in understanding lung hygiene and host defenses.

Little is known of the normal development of the lung, its biochemical maturation and histologic changes in aging. Therefore, the growth and aging of the lung should be studied. Investigation is also needed in lung embryology and teratology. Studies of the morphometry of lung tissue should permit consideration of the lung as an organ in terms of its biophysical responses. It will be necessary to analyze the chemical structure and physical properties of individual lung components. It will be important to explore the cellular biology and the molecular biology of uniform cell populations from human lung. The transport and membrane systems of the lung should be studied since a major function of the lung is to provide a means for gas exchange. It will also be important to characterize membrane functions of individual cell lines obtained from the lungs.

A number of classical areas of pulmonary physiology require continued study. These include studies of the mechanical properties of the ventilatory apparatus and the pulmonary vascular bed and the coupling of mechanical events to the neurophysiological regulation of ventilation. These studies should be performed with bioengineering collaboration to provide new insights.

The lung is exposed to a wide variety of potentially injurious inhaled agents. As a result, environmental factors are important in the pathogenesis of respiratory diseases. In addition, the pulmonary absorption of injurious agents may lead to disease in other organs.

Epidemiologic studies of populations whose lungs are exposed to toxic substances are needed to define the nature and magnitude of the environmental health hazards. Systems should be developed for surveying new industries with respect to possible environmental health hazards. These studies should be explored not only in bulk populations but also in younger age groups, particularly children.

It is clear that cigarette smoking represents a major environmental respiratory hazard. Information is needed concerning the mechanism of cigarette smoking damage.

Epidemiologic investigations based on prospective studies are required. Psychologic and sociologic studies concerned with the possible elimination of the smoking habit are needed. Such studies should have major emphasis on methods designed to reach young people before they begin to smoke. Continued search for safe cigarettes should be pursued. Studies of bronchial mucus and ciliary function (previously considered under the normal lung), since these are affected by environmental agents, should be emphasized.

There are promising new therapeutic agents potentially capable of reversing the harmful tissue effects of inhaled environmental or occupational pollutants. The investigation of these should be vigorously pursued.



Emphysema and chronic bronchitis are common and still increasing causes of both death and disability in this country. Because of their high mortality and extreme morbidity, emphysema and chronic bronchitis warrant particular attention.

Prospective, controlled epidemiologic studies are required to determine both the incidence and risk factors in the development of emphysema and chronic bronchitis. Evaluation of the role of infectious agents, climate, and geography, as well as occupation, is needed. It is also important to determine whether airway disease in infants and children predisposes to chronic obstructive lung disease in the adult.

Since smoking plays an important role in the pathogenesis of both diseases, the recommendations noted in the previous section are pertinent here.

The pathogenesis of these diseases should be approached at various levels. Recent investigations have shown that individuals who inherit a deficiency of a specific enzyme, α_1 -antitrypsin, are predisposed to develop emphysema. Genetic investigations using studies of α_1 -antitrypsin globulin deficiency as a model represent one approach to studying this. Extensive use of papain-induced emphysema in animals represents another. The basic studies of connective tissue metabolism and lung defense mechanisms previously described should be particularly rewarding for these two diseases.



Because emphysema and chronic bronchitis are usually irreversible by the time they are diagnosed, improved techniques and devices are needed to detect early biochemical, immunologic or physiologic abnormalities associated with development of these diseases. Bioengineering approaches should be particularly helpful in this respect.

Clinical trials of existing treatment modalities including bronchodilators, environmental control, mucolytic agents, oxygen, physiotherapy and breathing exercises are suggested.

The major disorder in this category is bronchiolitis. There is no general agreement even on the clinical criteria to be used in defining this disorder. Therefore, careful clinical evaluation, measurements of pulmonary function, radiologic evaluation, and extensive documentation of infectious background must be performed on a carefully selected large group of patients. This could be accomplished by a collaborative study involving a number of recognized authorities in the field. In addition, epidemiologic studies could provide the data for a more acceptable definition of this disease and the ability to distinguish it from other forms of pediatric obstructive respiratory disease (bronchial asthma, acute bronchitis, pneumonia).

Important basic information concerning the behavior of airways as a function of size and age in children is needed. The neural regulation of airways and their pharmacologic response in the young should be investigated.

The development of noninvasive techniques to measure lung and pulmonary vascular function in the young is of immediate importance. Controlled clinical trials should be conducted to evaluate the various treatment modalities such as mist, bronchodilators, antiinflammatory agents and oxygen.



Bronchial asthma is the most important disease in this category and represents an exceedingly common disorder affecting all age groups.

The incidence and etiology of allergic airway disease should be investigated through controlled prospective epidemiologic studies. In these studies major emphasis should be given to bronchial asthma. A major epidemiologic tool would be mass surveys to determine the incidence of elevated immunoglobulin E levels in the general population and to correlate elevated immunoglobulin E levels with the development of clinical disease. Likewise, the relationship of asthma to respiratory infections should be explored by epidemiologic surveys.

An important pathogenetic lead involves the release from lung cells of chemical mediators of airway reactivity, and these should be intensively studied. Continued search for additional mediators involved in asthma should be undertaken. Animal models should be developed to investigate these factors in vivo. Simple, accurate means of early detection and diagnosis using physiologic, biochemical and immunologic approaches should be investigated. Clinical trials of steroids, immunosuppressive agents (in treatment-failure patients) and antiinflammatory agents are needed.



This group of disorders constitutes the second most common form of chronic lung disease in adults. Because of the diverse etiologic background, exact incidence is difficult to estimate and epidemiologic studies must generally be retrospective and based on uncertain clinical criteria or on X-ray surveys.

For this reason, the development of animal models would be of particular importance. Careful exploration of potential etiologic factors (genetic, drugs, pulmonary vascular disorders, viral and other infectious agents) should be conducted.

Attempts to develop physiologic, biochemical and immunologic indicators of early interstitial disease are of great importance.

Since the end-stage of many of these disorders is the development of pulmonary fibrosis, studies of collagen and basement membrane metabolism (as previously discussed) would be of key importance. These diseases usually result from altered alveolar epithelial cell or pulmonary capillary endothelial cell abnormality. Therefore, studies of the metabolism of these cells should provide important pathogenetic information. Controlled clinical trials of corticosteroids and immunosuppressive agents are needed.

One major approach to the control of these diseases is increased understanding of both general host defense and specific lung defense mechanisms. Prospective controlled epidemiologic studies should be conducted to help determine host factors. The magnitude of fungal diseases in the United States is unknown and both epidemiologic studies and mandatory case reporting are needed in this area. These methods should also be applied to determine the magnitude of nonbacterial, nonviral lung infection. Study of lung cleansing mechanisms and immunologic mechanisms in animal models and in patients should also be conducted.

The development of simple, accurate means of diagnosis using such techniques as immunofluorescence or negative staining electron microscopy should have a high priority.

The treatment and management of infectious respiratory disease is in need of further study. In particular, immunoprophylaxis by means of vaccines represents a promising area.

Effective chemotherapeutic agents should continue to be emphasized with priority given to the development of antiviral agents.

The etiologies of sarcoid and granulomatous lung diseases should be investigated through the use of controlled prospective epidemiologic studies. Insight is needed into the role of genetic factors, dietary factors, environmental factors, and antecedant triggering diseases (infectious, environmental, etc.), variations in antibody responses, immunization, and underlying (preexisting) alterations in delayed type hypersensitivity. Pathophysiologic studies should be conducted, especially into the mechanism of foreign body reaction in various immunologic states.

In order to gain more knowledge about sarcoid and granulomatous lung diseases, animal models should be developed. The role of T-lymphocytes, B-lymphocytes, "transfer factor" and possible viral etiology should be clarified.

The detection and diagnosis of sarcoid lung disease is usually a diagnosis of exclusion. The Kveim test is controversial in regard to its accuracy in diagnosing sarcoid lung disease. Therefore, the role of the Kveim test should be established in the diagnosis of sarcoid. Also, new means of early detection and diagnosis for sarcoid and granulomatous lung diseases should be developed.

The present treatment modalities for sarcoid and granulomatous lung diseases should be evaluated through controlled, prospective clinical trials. The efficacy of transfer factor, immunosuppressive drugs, and corticosteroids need to be evaluated.

Knowledge of the incidence and etiology of these diseases will be substantially increased by prospective epidemiologic studies.

The development of appropriate animal models should be emphasized. Investigation of antigens responsible for these disorders should be accelerated and antigens should be standardized and commercially available. Specific and sensitive immunologic tests using serum and respiratory secretions should be developed. Antibody identification of these antigens by the development of sensitive techniques would be important.

Clinical trials are required to investigate the efficacy of corticosteroids and the efficacy of antigen avoidance. Further research is required to develop new anti-inflammatory agents.

3.10 PULMONARY VASCULAR DISEASES

3.10.1 Cor Pulmonale

Abnormal cardiac function should be studied in patients as a function of long- and short-term graded increases in pulmonary artery pressure in patients. These studies should involve functional measurements of left ventricular, as well as right ventricular, function.

Animal models should be developed to determine the effects of pulmonary hypertension, hypoxemia, hypercapnia and acid-base disturbances on cardiac function. Isolated heart cells should also be studied in this respect. Collaborative studies involving both cardiologists and chest physicians would be particularly helpful.

Clinical trials should be developed to compare the efficacy of various therapeutic approaches.

3.10.2 Pulmonary Hypertension

Prospective epidemiologic studies should be developed to determine the incidence of pulmonary hypertension in populations of patients with pulmonary disease. The development of noninvasive methods for measurement of pulmonary artery pressure would facilitate the application of such studies.

Animal models for pulmonary hypertension should be developed as indicated in the section on cor pulmonale.

Physiologic, biochemical and metabolic studies on pulmonary artery smooth muscle are required and these should be correlated with structural changes.

3.10.3 Pulmonary Edema

Controlled, prospective epidemiologic studies should be conducted in order to determine incidence and etiologies of pulmonary edema. Contributing factors and associated disorders which lead to pulmonary edema should be identified in clinical situations.

The basic pathophysiology and pathogenesis of pulmonary edema should be studied with regard to water content of lung and its compartmental distribution, metabolic changes in the edematous lung, defense mechanisms of edematous lung, characteristics of endothelial and epithelial barriers in terms of irreversible thermodynamics, effects of various agents on barrier characteristics, role of lymphatics, role of surfactant, clearance of lung liquid, and composition of pulmonary edema fluid.

New techniques and devices should be developed in order to determine the presence and extent of pulmonary edema. Approaches such as radiant energy absorption, ultrasound, holograms, and capacitance changes should be investigated.

Controlled clinical studies should be conducted to test the efficacy of various procedures and therapies. Significant research into new therapeutic agents such as dextran and prostaglandins is needed.

In order to define the population at risk for hyaline membrane disease of the newborn, prospective controlled epidemiologic studies should be conducted. Within these studies the effects of obstetric measures, the role of other maternal illness, and a possible genetic basis can be evaluated. Amniotic fluid should be studied especially in terms of its use in diagnosis and as a possible contributory factor. Of significant importance is the evaluation of methods to prevent premature birth. Those factors that predispose mothers to premature birth should be identified. Also, more research is needed into the mechanism of onset of labor.

Evaluation of supportive measures in the early neonatal period is of great importance especially in regard to the role of fetal and neonatal blood volume and the significance of deviations in vascular pressures. Important questions include: morphometry of immature diseased lung, biochemical abnormalities in lipids and proteins extracted from lungs; ultrastructural changes and histochemical events in alveolar cells and capillaries; biochemical events in developing primate lungs; pathways of lipid synthesis, relationship of intraventricular hemorrhage to lung disease; and ways in which immature lung repairs itself.

The early, simple and accurate detection of hyaline membrane disease of the newborn is of top priority. Evaluation of cord-blood proteins and enzymes as possible predictors of disease is very important.

In the treatment of hyaline membrane disease in the newborn, criteria should be identified for the definition of optimal care. Studies should include standardized clinical and pathological definitions, evaluations of the best means of transport of infants to therapy centers, evaluation of means to accelerate lung maturation, evaluation of pharmacologic agents, improved methods for assistance in respiratory support, evaluation of blood oxygenator, effects of alterations in blood volume on course of disease, and the role of increasing 2, 3-DPG levels in red cells.

Long-term follow-up studies should be conducted in order to evaluate the fate of survivors of hyaline membrane disease in the newborn. Especially important are follow-up on pulmonary and cerebral function and the incidence of late sequelae as a direct response to the type of prenatal and neonatal management.



Etiology and incidence of cystic fibrosis should be investigated through controlled, prospective epidemiologic studies. Techniques should be developed in the early, accurate and simple detection and diagnosis of cystic fibrosis. Investigation into methods for prenatal diagnosis and for identifying heterozygotes is important. Also, animal models should be developed for the study of cystic fibrosis.

The study of the pathophysiology and pathogenesis of cystic fibrosis is needed especially in regard to the biochemical abnormalities of cystic fibrosis. Such questions as ciliary dyskinetic factors of serum and saliva, factors affecting membrane function, pathophysiology of salivary glands and culture leukocytes should be investigated in attempting to gain further understanding of cystic fibrosis. Development of efficacious treatment and management of cystic fibrosis might include genetic counselling, therapeutic abortion of the fetus diagnosed as homozygote in utero, and research into the development of therapy at the molecular level. Controlled clinical studies should be conducted to evaluate present therapeutic methods for long-term treatment of cystic fibrosis.

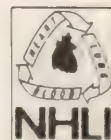
3.13 ACUTE AND CHRONIC RESPIRATORY FAILURE

The etiology, incidence and natural history of acute and chronic respiratory failure should be studied by prospective epidemiologic surveys. In the case of acute respiratory failure, an important approach involves lung function and blood gas measurements on a large population of trauma patients. Long-term follow-up of survivors of acute respiratory failure is also important to determine the incidence of irreversible lung changes.

The determination of the mechanisms of lung injury in acute and chronic respiratory failure is important and involves studies of lung cell permeability, lung defense mechanisms and lung cleansing mechanisms previously described.

Investigation is needed to develop methods of early detection as described in the section on pulmonary edema. Evaluation of current and new treatment modalities through prospective, controlled, clinical trials is necessary. Significant support should be given to the development of new modalities of treatment.

Of key importance to acute and chronic respiratory failure and also of importance to many respiratory diseases is the development of effective community emergency services.



Much of the morbidity and mortality of patients with respiratory disease arises as a result of impairment of nonpulmonary organs and cells. Emphasis on the extrapulmonary manifestations of respiratory disease are therefore of great importance.

The three major extrapulmonary manifestations are hypoxia, hypercapnia and acid-base disturbances. The effects of these in patients, in animal models and in cellular and subcellular systems require intensive study. Such studies will involve physiological, biochemical and biophysical approaches.

Clinical studies involving the therapy of these manifestations are needed as well as the development of suitable instrumentation for monitoring changes in these variables in an accurate and continuous fashion.

The recent demonstrations that the lung is involved in the biotransformation of a wide variety of systemically active humoral agents is of great potential importance. This area of work should be actively pursued.

Despite the enormous broadening of knowledge and interest in pulmonary diseases, relatively little attention has been given to the dissemination of this knowledge in an effective manner to the various groups who require it.

In the course of implementing an expanded lung program, a significant and purposeful education plan is required in order to fulfill the goals of prevention, detection and diagnosis, treatment and management, and rehabilitation. This should be directed not only at physicians and medical students but to allied health professionals, the public at large, patients themselves and their families.

Adequate numbers of scientific personnel are required to implement the scientific portions of this report. These include basic and applied scientists as well as physicians and allied health professionals. The specific manpower needs should be determined by careful analysis. Periodic review of these needs should be conducted so that these estimates can be revised in the face of changing needs.

The general public must be made aware of the causes and prevention of lung disease, its early signs and symptoms, the limitations it imposes and methods for the avoidance of environmental irritants with the potential of inducing lung damage.

Patients with respiratory disease rarely understand its implications and, in the chronic forms, the restrictions

it places upon them. This is no less the case with their families. A structured effort should be made to provide this knowledge.



PART IV

THE LEGISLATION AND THE PROPOSED PROGRAM



PART IV
THE LEGISLATION AND THE PROPOSED PROGRAM

Section 413 of the National Heart, Blood Vessel, Lung and Blood Act of 1972 delineates 10 areas of legislative requirements. This section correlates the proposed research efforts developed by the Lung Diseases Panel and its Task Groups with these 10 requirements. The 10 requirements are presented as a list in Appendix B.

It became apparent during the course of the work that it would be unproductive to attempt to precisely correlate the findings of the Panel with the requirements due to the inherent overlap in the prescribed categories and the overlap in the way the given Panel findings relate to these categories. With the single exception of education where the Panel found it could treat the requirements under the self-contained topic of Education in Lung Diseases, the remaining 14 Problem Areas respond in a relatively broad manner to the mandates of the legislation.



The following sections consider each requirement in turn, and indicate, in a representative manner, the character of the activities recommended by the Panel as they relate to each requirement.



4.1 LEGISLATIVE REQUIREMENT NO. 1

"... investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology and prevention of such diseases; ..."

4.1.1 The Normal Lung

Requirement not appropriate to this Problem Area.

4.1.2 Environmental Respiratory Diseases

Epidemiologic studies of population whose lungs are exposed to toxic substances are required. Included among the most pressing needs are: surveying new and rapidly developing technologies with respect to identification and control of possible environmental hazards; prospective studies of smoking and air pollution; determination of the submicroscopic particulate burden of community air; and studies of the importance of physical factors, e.g., high and low temperature, dry or wet atmosphere and radiation.

4.1.3 Emphysema and Chronic Bronchitis

Epidemiologic studies should be performed to determine both the incidence of, and potential etiologic factors in, emphysema and chronic bronchitis. The etiologic role of infectious agents, air pollution, smoking, nonoccupational and genetic factors, atmospheric, climatic and geographic factors should be evaluated. Investigations should be



conducted into the means by which risk factors can be eliminated or controlled. A clearer understanding of the basic pathophysiology in emphysema and chronic bronchitis would be enhanced by the development of models of these lung diseases. Epidemiologic studies should be conducted to determine the susceptibility to lung disease of individuals with various inheritance patterns of α_1 -antitrypsin.

4.1.4 Pediatric Obstructive Respiratory Diseases

A sharpened definition of syndromes, including family histories is needed. Other studies should explore the susceptibility of infants' lungs to pollutants and the natural course of respiratory diseases in childhood.

4.1.5 Allergic Airway Disease--Asthma

The incidence and etiology of allergic airway disease should be investigated through controlled, prospective epidemiologic studies. Individuals should be identified who have both high or low risk for atopic disease and have acquired allergic airway disease. Mass surveys of subjects with increased immunoglobulin E are of particular importance.

4.1.6 Diffuse Interstitial Respiratory Diseases

Precise etiologic factors need to be delineated so that optimal therapies can be developed, since the lung appears to respond in a similar way to a number of disease entities (as determined by light microscopy). Animal models are needed to determine the impact and action of suspect etiologic agents identified in epidemiologic investigations.

Drug histories for patients should be compared with currently available models of drug-induced interstitial lung disease; for example, radiation-produced interstitial lung disease provides a good animal model for a variety of studies including the role of antifibrogenic agents. Epidemiologic studies should also be directed toward the identification of common environmental factors among people developing disease since it is known that inhaled substances can produce interstitial disease (e.g., Berylliosis). Since risk factors in most interstitial diseases have not been identified, it is important (1) to determine how to control those that have been identified and (2) to identify other risk factors including genetic, allergic, and other altered immune responses.

4.1.7 Infectious Respiratory Diseases

Studies should be conducted to determine those host factors that modify infectious respiratory diseases. People who have a high incidence of infectious respiratory disease should be identified and risk factors determined.

Studies should be initiated to determine the magnitude of fungal diseases in the United States (perhaps assisted by the development of mandatory case reporting systems). Also, determination of the growth characteristics of fungi which colonize in humans will be important in developing effective treatment. The determination of the magnitude of non-bacterial, nonviral diseases is also needed (again assisted by the development of mandatory case reporting systems). The growth characteristics of *Pneumocystis carinii*, which allow colonization and disease in man, need to be studied so that effective treatment can be developed. At present,

much work is needed in defining the etiologies of different respiratory syndromes in children. Refinements in currently utilized methods to identify bacterial, viral, and mycoplasma infections or colonization should be developed. The application of newer modalities of diagnosis (such as organ culture, co-cultivation, radioimmunoassay, etc.) will result in advances toward understanding and treating these respiratory syndromes. Immunodeficiency disease should be investigated by epidemiologic studies.

4.1.8 Sarcoid and Granulomatous Lung Diseases

Insight is needed into the role of (1) genetic factors, (2) dietary factors, (3) environmental factors, (4) antecedent triggering diseases (infectious, environmental, etc.), (5) variations in antibody responses, (6) immunization, and (7) underlying (preexisting) alterations in delayed type hypersensitivity as etiologic factors in these diseases.

4.1.9 Hypersensitivity Lung Diseases

Incidence and etiology of hypersensitivity lung disease should be determined by prospective epidemiologic studies; longitudinal studies of natural history are of importance. Antigens need to be identified by screening suspected dusts. Animal models can be utilized to determine injury induced by exposure and reexposure.

4.1.10 Pulmonary Vascular Diseases

Studies should be conducted to identify extrinsic factors affecting pulmonary and vascular dysfunction; environmental



pollution as an extrinsic factor is of key importance. Epidemiologic studies should be conducted to determine the incidence and etiology of cor pulmonale, pulmonary hypertension and pulmonary edema.

4.1.11 Hyaline Membrane Disease of the Newborn

A more precise definition of the population at risk is needed. The work should include epidemiologic studies, the effects of obstetric measures, the role of maternal illness and the possible genetic basis of the disease.

4.1.12 Cystic Fibrosis

There should be work in the determination of the incidence of cystic fibrosis.

4.1.13 Acute and Chronic Respiratory Failure

The etiology, incidence and natural history of acute and chronic respiratory failure all need to be determined. Longitudinal studies of patients with respiratory distress syndromes should be conducted. Epidemiologic investigations are integral to an understanding of acute and chronic respiratory failure. Genetic and immunologic characteristics of survivors of respiratory distress syndromes will enable prediction and possible control of future outcomes.

4.1.14 Extrapulmonary Manifestations of Respiratory Diseases

Epidemiologic studies of the extrapulmonary manifestations of respiratory disease should be conducted on selected populations to identify (1) fetal wastage, (2) incidence of fetal abnormalities, (3) neonatal mortality, (4) growth and development over early years of life, and (5) adaptive changes which permit long-term residents at high altitude to produce viable offspring.

4.1.15 Education in Lung Diseases

Requirement not applicable to the Problem Area.



"... studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena; ..."

4.2.1 The Normal Lung

A major emphasis should be placed on studies of the normal lung because relatively limited information (particularly that concerning the cellular biology of the lung) is the primary constraint on the development of efficacious preventive, diagnostic and therapeutic modalities. Among the major proposals are studies concerning the quantities of connective tissue components in normal lung and differences in their distribution in various portions of the lung with (1) age, sex and environmental influences; (2) the amino acid composition of collagen and elastin in lung tissues, their chemical precursors and their possible variations with age, sex and environmental influence; (3) variations in quantity and amino acid composition of the connective tissue components of lung in diffuse pulmonary fibrosis and in various types of airway obstructive disease; (4) relationships of surface forces of alveoli to the mechanical characteristics of tissue components of the lung; (5) the kinetics of synthesis of elastin and collagen; and (6) the in vivo balance and interaction among proteolytic enzymes with potential for altering pulmonary connective tissue.

Pulmonary tissue substrates require full investigation including basic studies of collagen, basement membrane collagen, elastic fibers, and other protein components.



Investigation is required of:

- The imbalance between proteolytic activity and its control by inhibition
- Cellular turnover rates of functioning lung cells and the alteration in these turnover and replacement rates
- The structure, synthesis, physical and physico-chemical characteristics of bronchial mucus in health and disease
- Factors which control elasticity and viscosity of respiratory tract secretions
- The whole area of phospholipid and protein synthesis by the lung and its various cell types as well as the glycoprotein structure of the lung.

The normal development of the lung, its biochemical maturation and histologic changes in aging should be determined. Growth and aging of the lung parenchyma, the blood vessels and lymphatics, the factors associated with aging, and the establishment of normal values for lung function with aging should be studied.

Investigation is also needed in lung embryology and teratology. It will be important to use new ultrastructural and biophysical techniques to define the alterations of lung structure and lung function produced by disease. Studies of the morphometry of lung tissue should permit consideration of the lung in terms of its biophysical responses. It will be necessary to analyze the chemical structure and physical properties of individual lung components. These studies should be accompanied by chemical dissection of the lungs themselves, thus permitting studies of discrete materials obtained from the normal lung. The biochemical

studies should be correlated with the physical properties of the isolated material in order to compare this with diseased tissue.

It will be important to explore the cell and the molecular biology of uniform cell populations from the human lung. The transport and membrane systems of the lung should be studied since a major function of the lung is to provide a means for gas exchange. In order to do this, it will be important to characterize exchange and transport barriers in terms of irreversible thermodynamics. It will also be important to characterize membrane functions of individual cell lines obtained from the lungs. Investigation into ciliary function and structure will be crucial in developing knowledge of how these function with respect to lung hygiene and host defenses.

4.2.2 Environmental Respiratory Diseases

Studies should include cleansing mechanisms, ciliary action and quantitative studies of bronchial cellular change designed to investigate the determinants of individual responses, and these should be explored not only in the general population but in younger age groups. For example, the study of the natural history of pulmonary diseases in association with community air pollution should properly begin in childhood and should also take into account such factors as disease history, demography and nutrition.



4.2.3 Emphysema and Chronic Bronchitis

Pathophysiological studies of emphysema and chronic bronchitis including investigation into the changes in the control of mucus secretion, the defense mechanisms, and the lung's response to injury should be conducted. The relationship of the pathology caused by emphysema and chronic bronchitis should be understood in terms of the changes in pulmonary function. Research into cell turnover rates is of importance. Changes in surfactant, specifically turnover rates, the mechanism of clearance of surfactant and the quantitation of the amount present with regard to age, should be investigated.

The pathophysiology and pathogenesis of other genetic lung diseases should be studied especially in reference to α_1 -antitrypsin deficiency. The role of proteolytic substances in lung damage should be characterized and these substances should be identified. The relationship between liver, lung and other organ dysfunction in α_1 -antitrypsin deficiency should be investigated. Basic research into the effect of proteolytic enzymes on structural and metabolic features of the lung is necessary, as is characterization of other serum and tissue inhibitors of proteolysis.

4.2.4 Pediatric Obstructive Respiratory Diseases

Studies should be conducted on the behavior of airways as a function of size and age, including the neural regulation of airways, their pharmacologic response and reflex patterns between upper and lower airways.



4.2.5 Allergic Airway Disease--Asthma

The pathophysiology and pathogenesis of allergic airway disease must be delineated. Chemical mediators of airway activities should be studied especially concerning their mode of action, receptors and the means of blocking these receptors. Identification should be made of immunologic reaction patterns in different groups of patients. Studies should be conducted into constitutional differences in pharmacologic reactivity. Investigations into mucociliary transport, characterization of properties of abnormal mucus, function of mast cells, role of lymphocytes, adenylcyclase, and the role of the eosinophil will contribute much information to our understanding of allergic airway disease. Animal models should be developed in order to study many of the above questions and other aspects of allergic airway disease.

4.2.6 Diffuse Interstitial Respiratory Diseases

Specific pathophysiologic and pathogenetic areas of investigation include:

- The relationship of structure and function in Diffuse Interstitial Respiratory Diseases
- The relationship of biochemical function and alterations in metabolism to pathologic and physiologic changes
- Determination of the physiologic changes in various entities and the relationship of these to the above mentioned studies
- Identification of genetic variations in lung structure and function as they relate to development of interstitial disease



- Deviation from normal defense mechanism in the disease entities such as collagen and vascular disease in animal models
- The pathologic response to injury in animal models determined by longitudinal studies.

4.2.7 Infectious Respiratory Diseases

The study of lung defense mechanisms is important in the understanding of infectious respiratory diseases. Investigations into mucociliary transport and the characterization of properties of abnormal mucus are needed. The lymphatic pathways of the lung need elucidation. Factors which determine different inflammatory reactions in the lung need to be understood since the lung has various responses to different infectious agents. Infectious respiratory diseases affect both the upper and lower respiratory tract, and the interaction of the defense mechanisms of these two tracts needs further study.

Investigation into lymphocyte function, lymphocyte membrane characteristics, mediators of cellular immunity, humoral immune response, and their genetic mechanisms in immunodeficiency disease is important.

4.2.8 Sarcoid and Granulomatous Lung Diseases

Pathophysiologic studies should be conducted especially into the mechanism of foreign body reaction in various immunologic states. Animal models are needed to gain more knowledge about sarcoid and granulomatous lung diseases. The role of T-lymphocytes, B-lymphocytes, transfer factor and possible viral etiology should be clarified.

4.2.9 Hypersensitivity Lung Diseases

Investigations should be conducted into the pathophysiology of hypersensitivity lung diseases and should include the development of animal models and determination of the mechanisms by which inhaled antigens produce an immunogenic response.

4.2.10 Pulmonary Vascular Diseases

Abnormal cardiopulmonary function should be studied especially with regard to the effects of long- and short-term graded increases of pulmonary artery pressure. The pathophysiology and pathogenesis of pulmonary and vascular disorders resulting in cor pulmonale, pulmonary hypertension and pulmonary edema should be investigated. Physiologic, biochemical and metabolic changes in the hemodynamics and smooth muscle function should be studied.

Specific factors requiring investigation are: Water content of lung and its compartmental distribution, metabolic activities of normal and edematous lung, defense mechanisms of edematous lung, characteristics of endothelial and epithelial barriers in terms of irreversible thermodynamics, effects of various agents on barrier characteristics, role of lymphatics, role of surfactant, clearance of lung liquid, and composition of alveolar fluid.

4.2.11 Hyaline Membrane Disease of the Newborn

Studies of biological processes to facilitate prenatal diagnosis should be undertaken. Work with postmortem materials and animal models should be carried out as part of the investigatory process.

4.2.12 Cystic Fibrosis

Studies of the biochemistry of cystic fibrosis should be conducted and include investigation in such areas as ciliary dyskinetic factor(s) in serum and saliva, the factor(s) affecting membrane function, and the pathophysiology of the exocrine glands. The lung defense mechanisms in cystic fibrosis should also be studied and include: mucociliary clearance, the role of the alveolar macrophage, immunologic defenses against infection and the roles of pulmonary perfusion and lymphatic drainage.

4.2.13 Acute and Chronic Respiratory Failure

The determination of the mechanisms of lung injury in acute and chronic respiratory failure is critical. In addition, investigations into the repair mechanisms of the lung will lend much to our understanding of the course of acute and chronic respiratory failure. Long-term assessments are needed to evaluate patients recovering from respiratory distress syndromes. Collagen and other connective tissue should be studied in terms of metabolism and cell function. Study is needed in the alteration and morphology in function of lung cells as repairs proceed.



4.2.14 Extrapulmonary Manifestations of Respiratory Diseases

Investigation into the effects of hypoxia, hypercapnia, and acidosis should include the adverse effects of ventilatory therapy in lung diseases on cerebral circulation, metabolism and function. Studies should also address the adjustments of cerebral circulation, cerebrospinal fluid and brain extracellular fluid to abnormal blood gases, the mechanism of brain dysfunction during hypoxia, the mechanism and treatment of brain edema in chronic lung disease, and the mechanism and prevention of CO₂ narcosis produced by oxygen therapy. Other studies should address pharmacologic agents used in lung disease, the brain ECF acid-base balance and alteration by lung disease, and the effect of chronic lung disease on the brain dysfunction of the aged.

Laboratory studies on the influence of hypoxia, hypercapnia and acidosis on growth and development of the newborn should include studies on placental function, placental development, enzymatic and cellular changes in the fetus and adaptive changes in acute and chronic exposures to hypoxia, hypercapnia and acidosis. Other studies should consider the various types of acidosis and their different effects, as well as the role of hypoxia, hypercapnia and acidosis in the genesis of abnormalities such as hyaline membrane disease.

Investigation into cellular biochemical abnormalities produced by hypoxia, hypercapnia and acidosis should include the improvement of techniques for in vivo and in vitro determinations, evaluations of morphological and membrane alterations, changes in steady state fluxes in response to low

oxygen tension, assessment of intracellular milieu in acute and chronic alterations, determination of abnormal levels of cellular constituents, causes of cell death and degeneration, biochemical relations in cellular adaptations, primary versus secondary effects, effectiveness of pharmacologic agents on cellular metabolism, patterns of enzyme adaptation in response to hypoxia, hypercapnia, and acidosis, cellular ionic regulation, and effects on metabolism due to changes in intracellular and extracellular pH.

Studies on humoral agents should be conducted in reference to the lung as an organism which synthesizes, degrades, inhibits, and accentuates certain humoral agents. These studies should include investigation into the biosynthesis and release of bioactive agents, metabolism of agents, pharmacologic agents, and biotransformation of exogenous compounds of the lung.

The biochemical aspects of tissue metabolism in high altitude dwellers should be studied. These studies should include the hematological control during high altitude adaptation, cellular and metabolic adaptations to high altitudes, vascular adaptation at high altitudes, pharmacologic responses in high altitude dwellers, genetic factors in response to high altitude hypoxia, enzyme adaptation in high altitude dwellers and cellular chemical changes in response to high altitude.

4.2.15 Education in Lung Diseases

Requirement not applicable to this Problem Area.

"... research into the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases; ..."

4.3.1 The Normal Lung

Requirement not appropriate to this Problem Area.

4.3.2 Environmental Respiratory Diseases

The use of chemical agents which reverse the harmful tissue effects of inhaled environmental or occupational pollutants requires investigation. For example, studies using polypyridine-N-oxide to prevent the fibrogenesis of silica, and the use of vitamin E to counter the pulmonary effects of oxidant gases are suggested.

4.3.3 Emphysema and Chronic Bronchitis

Biochemical, immunologic and physiologic techniques should be explored for the detection of presymptomatic disease. The present treatment modalities for emphysema and chronic bronchitis should be critically and thoroughly evaluated including the efficacy of mechanical devices and prolonged oxygen therapy. Investigation should also be conducted into improvement and simplification of methods for quantitating and phenotyping α_1 -antitrypsin deficiency as an aid to early, simple and accurate diagnosis.

Studies of potential replacement therapy, methods for α_1 -antitrypsin induction (liver) and tissue transplantation should also be conducted. Environmental control including the effectiveness of avoidance of smoking, avoidance of occupational and atmospheric irritants, effects of prevention and early treatment of respiratory infections in progress of lung damage in α_1 -antitrypsin deficiency should be thoroughly studied. Ancilliary tests, such as pulmonary function tests and ventilation and perfusion lung scans, should be evaluated in terms of their effectiveness in diagnosing α_1 -antitrypsin deficiency disease.

4.3.4 Pediatric Obstructive Respiratory Diseases

The development of noninvasive techniques to measure lung and pulmonary vascular function in the young is needed.

4.3.5 Allergic Airway Disease--Asthma

The development of simple accurate means of early detection and diagnosis of allergic airway disease should include investigation into pulmonary function tests and response to bronchodilators, methacholine challenge tests, and sputum examination for eosinophils. More research is needed into the identification of atopic abnormalities by skin test and in vitro studies of reagin. Evaluation and development of pharmacologic agents will be important in furthering more efficacious treatment. The evaluation of immunologic therapy, including hyposensitization and corticosteroids, is also needed.



4.3.6 Diffuse Interstitial Respiratory Diseases

Efforts must be made to improve the sensitivity of currently available diagnostic tests, such as the chest X-ray, for early detection of disease. Efforts should also be made to improve the diagnostic effectiveness of the chest X-ray, utilizing, for example, computer analysis of densitometry readings and exposure variation and the calculation of dose and exposure factors.

Biopsy material is currently the only way to establish the diagnosis of interstitial lung disease and work should be continued on improving needle biopsy techniques. Open lung biopsies offer the possibility of obtaining fairly large specimens of tissue on which extensive investigation can be performed along the lines mentioned earlier.

Except for steroids and antimetabolite drugs, there is little therapy currently available for the interstitial respiratory diseases. It is important, then, to evaluate the role of corticosteroids through studies in humans and animal models and also to evaluate immunosuppressive therapy in carefully controlled, randomized, prospective studies. Although physiologic measurements have been used to gauge the effectiveness of the therapy, examination of cellular characteristics, immunologic competence, and the biochemistry of expectorated alveolar cells may merit investigation.

4.3.7 Infectious Respiratory Diseases

The development of simple, accurate means of diagnosis is of top priority. More effective serological tests need to be

developed. Also, the differentiation between colonization within the hospital and infection is needed. Further study into rapid mechanisms for diagnosis, possibly utilizing immunofluorescence or negative staining electron microscopy, is needed. The treatment and management of infectious respiratory diseases is also in need of further study. Immunoprophylaxis development is of top priority since vaccines for a number of infectious agents remain to be developed. Of significant aid will be the purification of the immunogenic components of the tubercle bacillus in order to develop an effective tuberculosis vaccine.

The development of effective chemotherapeutic agents in infectious respiratory diseases is also of high priority. Further work needs to be conducted on the development of antiviral and antifungal agents and the development of effective antimicrobials for resistant bacteria.

Early, accurate, simple means for detection and diagnosis of immunodeficiency disease is important. Development of screening services for study of cord blood lymphocytic and phagocytic functions should aid in this early recognition. Uniform screening tests for antigens in the assessment of cellular immune functions should be developed. More research is needed in order to develop accurate and sensitive methods for detecting immunodeficiency disease.



Treatment and management of immunodeficiencies center around the areas of immunologic reconstitution, replacement therapy and the application of germ-free isolators. Studies in immunologic reconstitution should include:

- Development of in vitro models for the study of immunologic enhancement
- Characterization of enhancing antibody factors
- Studies of conditions favoring development of enhancement antibodies
- Comparative study of HL-A responsiveness in immunodeficiency families
- Evaluation of immunocompetent cells from different sources in restoring immunocompetence
- Biochemical and biological characterization of transfer factor
- Evaluation of transfer factor therapy in immunodeficiency disease.

Study of replacement therapy in the immunodeficiencies should include:

- Development of more effective ways of preparing gamma globulin suitable for intravenous infusion
- Evaluation of safety and efficacy of plasma therapy in immunodeficiency through use of a single donor
- Development of hepatitis antigen-free plasma banks for therapy of immunodeficiency.

4.3.8 Sarcoid and Granulomatous Lung Diseases

The detection and diagnosis of sarcoid lung disease is usually a diagnosis of exclusion. The Kveim test is controversial in regard to its accuracy in diagnosing sarcoid lung disease, and its role as a testing modality should be established. Also, there should be development of new means of early detection and diagnosis for sarcoid and granulomatous lung disease. Development of new modes of therapy are also important and appropriate research projects should be developed.

4.3.9 Hypersensitivity Lung Diseases

There is a need for the development of simple, accurate means of detection and diagnosis in hypersensitivity lung diseases. Antigens should be standardized and commercially available. Specific and sensitive immunologic tests of serum and respiratory secretions should be developed and become clinically available. Further research is needed in the development of specific antiinflammatory agents and in the development of new therapeutic agents.

4.3.10 Pulmonary Vascular Diseases

The development of techniques and devices for simple, accurate diagnosis of pulmonary abnormalities is important in cor pulmonale. Single breath tests of respiratory function in minimally cooperative patients would be a great advantage and deserve significant investigation.

Techniques and devices should be developed for simple, accurate detection in the diagnosis of pulmonary hypertension. Major emphasis on noninvasive determination of pulmonary artery pressure would be most useful.

New techniques and devices should be developed in order to determine the presence and extent of pulmonary edema. Indicator dilution techniques may be appropriate and new technologic advances can be utilized in developing procedures such as radiant energy absorption, ultrasound, holograms, capacitance changes or other techniques for the early detection and diagnosis of pulmonary edema. Significant research into new therapeutic agents such as dextran and prostaglandins should be supported.

4.3.11 Hyaline Membrane Disease of the Newborn

There should be studies to improve the tools used in early diagnosis, including the evaluation of cord-blood proteins and enzymes as predictors of the disease and the search for new indicators in maternal blood, amniotic fluid and urine.

4.3.12 Cystic Fibrosis

Methods are needed for identifying the heterozygote and for the interpretation of this information in genetic counseling. Therapy should be developed at the molecular levels.

4.3.13 Acute and Chronic Respiratory Failure

Investigation is needed in order to develop the means for early detection and diagnosis of respiratory distress

syndromes. Improved methods should be found for monitoring blood oxygen. Assessment of the sequential appearance of other physiological parameters should also be studied.

Significant support should be given to the development of new modalities of treatment and management of acute and chronic respiratory failure including use of electrical stimulation of the phrenic nerve in some forms of failure.

4.3.14 Extrapulmonary Manifestations of Respiratory Diseases

There should be studies for:

- Development of agents and approaches to augment blood oxygen transport during hypoxia
- Augmentation of enzymatic support of anaerobic glycolysis to improve energy supply during hypoxia
- Augmentation of enzymatic support of oxidative phosphorylation to improve efficiency of oxygen utilization
- Development of agents and approaches to reverse abnormal redox states
- Tailoring of tissue metabolic needs and tissue responses to decreased oxygen supply
- Development of nongaseous forms of systemic oxygen administration.

4.3.15 Education in Lung Diseases

Requirement not applicable to this Problem Area.

"... establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases; ..."

4.4.1 The Normal Lung

A number of classical areas of pulmonary physiology require continued study. These include studies of the mechanical properties of the ventilatory apparatus and the pulmonary vascular bed and the coupling of mechanical events to the neurophysiological regulation of ventilation. These studies should be performed with bioengineering collaboration to provide new insights.

4.4.2 Environmental Respiratory Diseases

Development of more sensitive and specific tests for detection of early disease of the lung will draw substantially upon bioengineering technology.

4.4.3 Emphysema and Chronic Bronchitis

Bioengineering technology will be of key importance in the development of new and more sensitive diagnostic devices and in the development of more efficacious treatment devices.

4.4.4 Pediatric Obstructive Respiratory Diseases

Means for safer radiologic examination with or without contrast media is needed.

4.4.5 Allergic Airway Disease--Asthma

Covered in other Problem Areas.

4.4.6 Diffuse Interstitial Respiratory Disease

There is a need for development of new techniques for obtaining and interpreting chest roentgenograms.

4.4.7 Infectious Respiratory Diseases

The application of germ-free isolators in the management of immunodeficiency will require the development of more practical and simpler germ-free isolation units for:

- Study of the growth and development of immunodeficiency patients
- Study of the psychosocial effects of germ-free isolation in immunodeficiency patients
- Microbiological monitoring of the effectiveness of various germ-free isolation units
- The study of morbidity and mortality rates in immunodeficiency patients maintained in germ-free isolation units.

4.4.8 Sarcoid and Granulomatous Lung Diseases

Covered in other Problem Areas.

4.4.9 Hypersensitivity Lung Diseases

There is a need for development of more sensitive techniques such as counter-immuno-electrophoresis to identify antibodies.

4.4.10 Pulmonary Vascular Diseases

Instrumentation should be developed through the utilization of bioengineering technology to detect and identify agents and factors associated with respiratory damage. Development of life support mechanisms for patients with severe cor pulmonale is very important and extracorporeal oxygenators and the possibility of extrapulmonary oxygen administration. could play a vital role in treatment.

4.4.11 Hyaline Membrane Disease of the Newborn

Improved means for transport of infants and improved methods of assisted respiratory support should be sought.

4.4.12 Cystic Fibrosis

Covered in other Problem Areas.

4.4.13 Acute and Chronic Respiratory Failure

Earlier detection of respiratory failure is important and needs further study. Bioengineering technology will be integral to this area of investigation.

4.4.14 Extrapulmonary Manifestations of Respiratory Diseases

Instrumentation should be developed for monitoring changes in lung function during oxygen inhalation.

4.4.15 Education in Lung Diseases

Requirement not applicable to this Problem Area.

4.5 LEGISLATIVE REQUIREMENT NO. 5

"...establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases;..."

4.5.1 The Normal Lung

Requirement not appropriate to this Problem Area.

4.5.2 Environmental Respiratory Diseases

Field studies are needed to estimate the risk of smoking tobacco or similar substances on respiratory diseases, to assess the possible synergism of smoking with other environmental factors, to evaluate the effect of tobacco smoke pollution in public places on nonsmokers and to evaluate asymptomatic smokers to identify the factors that protect them. Additional field tests are needed for the development of screening tests for early detection of lung disease in occupational groups and for the evaluation of various rehabilitation regimens.

4.5.3 Emphysema and Chronic Bronchitis

Clinical studies should be conducted to validate and test the accuracy of recently developed tests for pulmonary functions.

Clinical trials need to be conducted on the effects of various drugs including bronchodilators, antibiotics, and mucolytic agents.



Clinical studies should be performed to evaluate the need of measuring α_1 -antitrypsin in amniotic fluid, cordblood and other body fluids.

4.5.4 Pediatric Obstructive Respiratory Diseases

Trials are needed for the evaluation of pharmacologic agents, including autonomic drugs, oxygen therapy, antiinflammatory agents, expectorants and other bronchodilators.

4.5.5 Allergic Airway Disease--Asthma

Controlled clinical trials of current methods of treatment of status asthmaticus and the identification of optimal treatment methods should be undertaken.

4.5.6 Diffuse Interstitial Respiratory Diseases

Improved immunologic studies are needed in patients and biopsy material regarding cell mediated immunity autoantigens, the competence of lymphocytes and the localization of immunoproteins in pathological specimens. There is a need for evaluation of treatment modalities including the role of corticosteroids, clinical trials of promising agents and evaluation of immunosuppressive therapy.

4.5.7 Infectious Respiratory Diseases

Clinical studies should be conducted to determine the shortest possible treatment time for tuberculosis.

4.5.8 Sarcoid and Granulomatous Lung Diseases

The present treatment modalities for sarcoid and granulomatous lung diseases should be evaluated through controlled, prospective clinical trials. The efficacy of the transfer factor, immunosuppressive drugs and corticosteroids need to be evaluated.

Long-term clinical studies of sarcoid and granulomatous diseases will be particularly important.

4.5.9 Hypersensitivity Lung Diseases

Clinical studies on the efficacy of skin testing with antigens in the diagnosis of hypersensitivity lung diseases should be carried out.

Controlled, prospective clinical trials should be conducted with corticosteroids in order to investigate their efficacy in the treatment of hypersensitivity lung diseases.

Clinical field studies should be conducted to determine the effects of the avoidance of antigens.

4.5.10 Pulmonary Vascular Diseases

Controlled, prospective clinical trials should be developed in order to compare the efficacy of different therapeutic approaches in cor pulmonale.

Clinical screening studies should be conducted in order to identify persons present with symptoms of early pulmonary hypertension.

Controlled clinical studies should be conducted in order to test the efficacy of various procedures and therapies in different clinical situations of pulmonary edema. The effects of decreased venous return, vasoactive and cardiac drugs, and various types of controlled respiration and oxygenation should be studied.

4.5.11 Hyaline Membrane Disease of the Newborn

Field studies are needed to establish criteria for optimal care including evaluation of pharmacologic agents, evaluation of blood oxygenators, effect of alteration of blood volume. Other field studies should be directed toward evaluation of the fate of survivors of the disease, including follow-up of pulmonary and vascular function and immune status.

4.5.12 Cystic Fibrosis

Field studies should be directed toward the evaluation and improvement of therapeutic methods for long involvement.

4.5.13 Acute and Chronic Respiratory Failure

Prospective, controlled, clinical trials are needed for the evaluation of current and new treatment modalities such as corticosteroids, bronchodilators, digitalis and diuretics, antimicrobials, mucolytic aerosols, humidifying aerosols, oxygen therapy, removal of irritants, mechanical ventilators, and membrane oxygenators.

4.5.14 Extrapulmonary Manifestations of Respiratory Diseases

Clinical studies should be conducted concerning the treatment of hypoxia. These studies should include the identification of the changes in pulmonary structure and function produced by high oxygen inhalation and the effect of high oxygen inhalation on organs other than the lung.

4.5.15 Education in Lung Diseases

Requirement not appropriate to this Problem Area.

4.5.16 All Disease Areas

As a commonly shared concern in all the disease areas, there should be evaluation of various rehabilitation, regimens involving consideration for the roles of physical and occupational therapy, exercise and psychological support. In addition, there should be development of models of comprehensive rehabilitation programs.

"...studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products;..."

Since two Panels were established by the National Heart and Lung Institute to advise on the problems of Blood Resources and Blood Diseases, no specific program recommendations were developed in this area by the Panel on Lung Diseases.



"...the education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases;..."

The perceived requirements regarding education and training of personnel are discussed in Section 2.15 of this report, entitled "Education in Lung Diseases."

"...public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources;..."

The requisite programs related to public and professional education regarding lung diseases are discussed in Section 2.15 of this report, entitled "Education in Lung Diseases."

"...establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases;..."

4.9.1 The Normal Lung

There is a need to identify the changes with maturation of the lung ultrastructure, the changes with maturation of lung components and the normal values for functions of the lung with development.

4.9.2 Environmental Respiratory Diseases

Prospective studies of population at various ages, particularly children, exposed to different types of pollutants and various physical factors (temperature, humidity).

4.9.3 Emphysema and Chronic Bronchitis

Determination of the susceptibility of individuals with various inheritance patterns of α_1 -antitrypsin. Evaluation of the need for measurement of α_1 -antitrypsin in amniotic fluid, cord blood and other body fluids.

4.9.4 Pediatric Obstructive Respiratory Diseases

The definitions of the syndromes causing upper and lower respiratory obstructive diseases in children need more resolution. Epidemiologic studies need to be conducted in order to obtain these more accurate definitions. These epidemiologic studies will also enable prediction of risk factors.

Studies of the susceptibility of infants' lungs to air pollutants are also of great interest and potentially great importance.

It is also important to clarify the contribution made by infectious agents through epidemiologic studies and clinical studies. Investigations into the behavior of airways as a function of size and age in upper and lower respiratory obstructive diseases in children should be undertaken.

Neural regulation of airways and the pharmacologic response of airways should be investigated. The effects of temperature, humidity and mist on the behavior of airways in the pediatric age group is needed. The detection and diagnosis of upper and lower respiratory obstructive diseases in children will be aided by the development of noninvasive methods to study lung function and pulmonary vascular function. Safer radiologic examinations with or without contrast media should also be developed.

The clinical measurement of physiological derangements, the documentation of biologic findings, and the assessment of radiographic findings should be combined to provide improved definition of these diseases.



Clinical field studies should be conducted to evaluate various modes of treatment and management. Pharmacologic agents such as autonomic drugs, antiinflammatory agents, expectorants, and bronchodilators should be evaluated. Also, oxygen therapy in these diseases should be evaluated by clinical study.

4.9.5 Allergic Airway Disease--Asthma

Genetic studies of etiology and pathogenesis in families and twins should be conducted and patterns of incidence should be established.

4.9.6 Diffuse Interstitial Respiratory Diseases

Requirement is not directly appropriate to this Problem Area.

4.9.7 Infectious Respiratory Diseases

Study of host factors that modify infection should be conducted. There should be development of means for early recognition of immunodeficiency as well as studies of immunologic reconstitution.

4.9.8 Sarcoid and Granulomatous Lung Diseases

Requirement is not directly appropriate to this Problem Area.

4.9.9 Hypersensitivity Lung Diseases

Requirement is not directly appropriate to this Problem Area.

4.9.10 Pulmonary Vascular Diseases

Requirement is not directly appropriate to this Problem Area.

4.9.11 Hyaline Membrane Disease of the Newborn

Controlled, prospective epidemiologic studies should be conducted in order to define the population at risk for hyaline membrane disease of the newborn. Within these studies the effects of obstetric measures, the role of other maternal illness, and a possible genetic basis should be evaluated. The amniotic fluid should be studied, especially in terms of its use in diagnosis and as a possible contributory factor. Factors that predispose mothers to premature birth should be identified. Important pathophysiological questions with respect to this disease include: morphometry of immature diseased lung, biochemical abnormalities in lipids and proteins extracted from lungs, ultrastructural changes and histochemical events in alveolar cells and capillaries, biochemical events in developing primate lungs (especially pathways of lipid cells and synthesis), the relationship of intraventricular hemorrhage to lung disease, and ways in which the immature lung repairs itself.

Of significant importance is the evaluation of methods to prevent premature birth. Evaluation of supportive measures in the early neonatal period is of great importance especially in regard to the role of fetal and neonatal blood volume and the significance of deviations in vascular pressures. Studies should be conducted in order to ascertain the effectiveness of resuscitation. The early, simple, and accurate detection of hyaline membrane disease of the newborn



is of top priority. Evaluation of cord-blood proteins and enzymes as possible predictors of disease is very important. A widespread search should be made for new indicators of the likelihood of disease by evaluating maternal blood, amniotic fluid, and urine.

In the treatment of hyaline membrane disease in the newborn, criteria should be identified for optimal care. Studies should include standardized clinical and pathological definitions, evaluation of the best means of transport of infants to therapy centers, evaluation of means to accelerate lung maturation, evaluation of pharmacologic agents, improved methods for assistance in respiratory support, evaluation of blood oxygenators, effects of alterations in blood volume on the course of disease, and the role of increasing 2, 3-DPG levels in red cells.

Long-term follow-up studies should be conducted in order to evaluate the fate of survivors of hyaline membrane disease in the newborn. Especially important is follow-up on pulmonary and cerebral function and on the incidence of late sequelae as a direct response to the type of prenatal and neonatal management. Also, follow-up studies should be conducted on the immune status of survivors.

4.9.12 Cystic Fibrosis

Etiology and incidence of cystic fibrosis should be investigated through controlled, prospective epidemiologic studies and through animal models. The study of the pathophysiology and pathogenesis of cystic fibrosis are needed especially in regard to the biochemical abnormalities of cystic fibrosis

Such questions as ciliary dyskinetic factors of serum and saliva, factors affecting membrane function, pathophysiology of salivary glands, in vitro analysis of skin fibroblasts, in vitro trachea bronchial tissue explants, and cultured leukocytes should be investigated in attempting to gain further understanding of cystic fibrosis.

Research into lung defense mechanisms in cystic fibrosis is also of key importance. This research should include study into mucociliary clearance, the role of the alveolar macrophage, immunogenic defenses against infection, the incidence of immediate hypersensitivity reactions, the role of pulmonary perfusion, lymphatic drainage, environmental influences, the role played by lower respiratory infections, and effects on the normal humidification of inspired air in the nose, throat, trachea and major bronchia.

Techniques should be developed for early, accurate and simple detection and diagnosis of cystic fibrosis; prenatal diagnosis and heterozygotes identification are important.

Development of efficacious treatment and management of cystic fibrosis might include genetic counseling, therapeutic abortion of the fetus diagnosed as homozygote in utero, and research into the development of therapy at the molecular level.

Controlled clinical studies should be conducted to evaluate present therapeutic methods for long-term treatment of cystic fibrosis.

4.9.13 Acute and Chronic Respiratory Failure

Covered by Problem Area 4, Pediatric Obstructive Respiratory Diseases.

4.9.14 Extrapulmonary Manifestations of Respiratory Diseases

Laboratory studies of the influence of hypoxia, hypercapnia and acidosis on the growth and development of the newborn.

4.9.15 Education in Lung Diseases

Requirement not applicable to this Problem Area.

"...establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services;..."

The development of effective community emergency services is of key importance to acute and chronic respiratory failure. Emergency facilities, such as emergency rooms and respiratory care units, and emergency medical techniques must be evaluated as to their efficiency in handling respiratory emergencies. Standards for equipment and personnel requirements need to be developed and, in conjunction with bio-engineering developments, model systems should be established and evaluated in diverse demographic areas.



APPENDIX A

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APPENDIX B

PROJECT AREA DISTRIBUTION ANALYSIS



APPENDIX B
PROJECT AREA DISTRIBUTION ANALYSIS

This appendix presents two categories of data displays resulting from analysis of project areas identified by each task group:

- The percentage distribution of project areas with respect to the 10 legislative requirements and
- The percentage distribution of project areas with respect to the four program objectives.

These results were obtained by a subjective comparison of each project area against the legislation requirements and objectives. These distributions do not reflect the relative manpower or funding required in any objective or legislative category since they are based only on the number of project areas identified.



1. Distribution of Project Areas with Respect to the Legislation

Table B-1 presents, on a problem area basis, the percentage of project areas which relate to the specific legislative planning requirements. The percentage distribution for all the problem areas as a composite is shown in Figure B-1.

The 10 legislative requirements are as follows:

"... (1) investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;

"(2) studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena;

"(3) research into the development, trial and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases;

"(4) establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases;



"(5) establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases;

"(6) studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products

"(7) the education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases;

"(8) public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources;

"(9) establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases; and

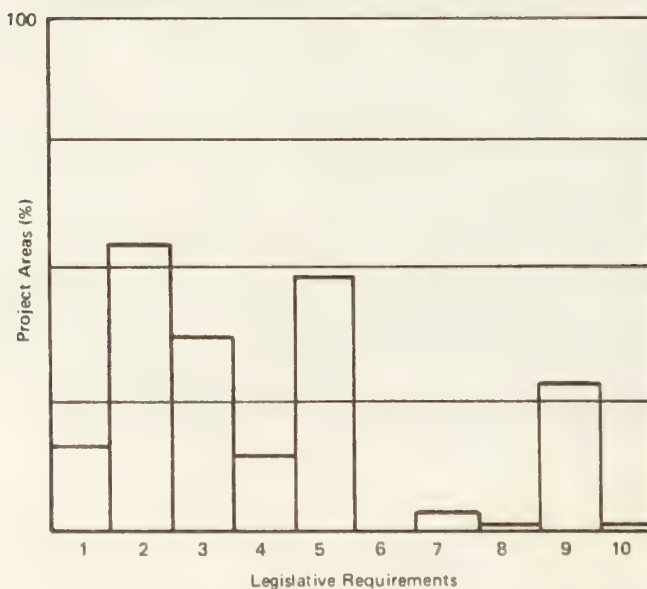
"(10) establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services..."

Table B-1
DISTRIBUTION OF PROJECT AREAS WITH RESPECT
TO THE LEGISLATIVE REQUIREMENTS

Problem Areas	No. of Project Areas	Legislative Requirement									
		1	2	3	4	5	6	7	8	9	10
The Normal Lung	44		100%								
Environmental Respiratory Diseases	28	43%	25%	32%	18%	71%				23%	
Emphysema and Chronic Bronchitis	43	14%	51%	42%	12%	47%				42%	
Pediatric Obstructive Respiratory Diseases	21	14%	24%	67%	14%	76%				100%	
Allergic Airway Disease-Asthma	26	15%	46%	54%	4%	50%					
Diffuse Interstitial Respiratory Diseases	21	38%	33%	52%	5%	71%					
Infectious Respiratory Diseases	52	11%	61%	39%	7%	54%				37%	
Sarcoid and Granulomatous Lung Diseases	15	27%	73%	53%	13%	67%					
Hypersensitivity Lung Diseases	19	16%	37%	63%		84%					
Pulmonary Vascular Diseases	43	12%	42%	37%	23%	53%					
Hyaline Membrane Disease of the Newborn	28	18%	36%	29%	11%	71%				100%	
Cystic Fibrosis	23	35%	65%	26%		44%				100%	
Acute and Chronic Respiratory Failure	29	3%	14%	52%	21%	76%				17%	17%
Extra-Pulmonary Manifestations of Respiratory Diseases	53	11%	83%	21%	6%	17%				6%	
Education in Lung Diseases	15							87%	13%		
TOTAL	460	15%	52%	35%	10%	48%		3%	1%	28%	1%

Figure B-1

COMPOSITE FOR ALL PROBLEM AREAS



KEY:

- 1 — Epidemiology, Etiology
- 2 — Biological Processes
- 3 — Techniques, Drugs, Devices
- 4 — Bioengineering
- 5 — Field/Clinical Studies
- 6 — Blood Resources
- 7 — Specialist Education
- 8 — Public Education
- 9 — Childhood Diseases
- 10 — Emergency Services

2. Distribution of Project Areas with Respect to the Program Objectives

Table B-2 presents, on a problem area basis, the percentage of project areas which relate to the four primary program objectives. The percentage distribution for all the problem areas as a composite is shown in Figure B-2.

These four objectives are:

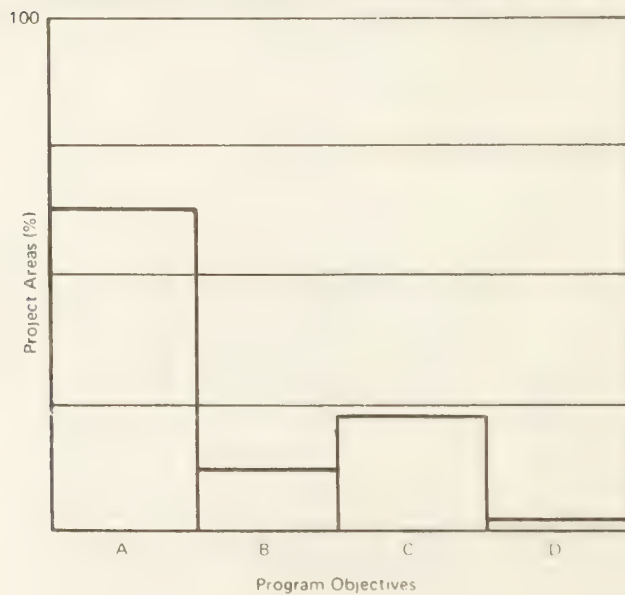
- A. Prevention
- B. Detection and Diagnosis
- C. Treatment and Management
- D. Rehabilitation.



Table B-2
DISTRIBUTION OF PROJECT AREAS WITH RESPECT
TO THE PROGRAM OBJECTIVES

Problem Area	No. of Project Areas	Primary Program Objectives			
		A	B	C	D
The Normal Lung	44	100%			
Environmental Respiratory Diseases	28	68%	7%	7%	18%
Emphysema and Chronic Bronchitis	43	51%	19%	30%	
Pediatric Obstructive Respiratory Diseases	21	62%	14%	24%	
Allergic Airway Disease-Asthma	26	54%	15%	31%	
Diffuse Interstitial Respiratory Diseases	21	67%	14%	19%	
Infectious Respiratory Diseases	52	33%	26%	41%	
Sarcoid and Granulomatous Lung Diseases	15	53%	13%	27%	7%
Hypersensitivity Lung Diseases	19	53%	21%	26%	
Pulmonary Vascular Diseases	43	58%	21%	21%	
Hyaline Membrane Disease of the Newborn	28	54%	7%	28%	11%
Cystic Fibrosis	23	70%	13%	17%	
Acute and Chronic Respiratory Failure	29	14%	6%	66%	14%
Extra-Pulmonary Manifestations of Respiratory Diseases	53	100%			
Education in Lung Diseases	15	100%			
TOTAL	460	63%	12%	22%	3%

Figure B-2
COMPOSITE FOR ALL PROBLEM AREAS



KEY:

- A — Prevention
- B — Detection and Diagnosis
- C — Treatment and Management
- D — Rehabilitation

APPENDIX C

DATA SUMMARY



APPENDIX C
DATA SUMMARY

This appendix provides a summary of the data base, i.e., the problems, approaches and project areas, which resulted from extensive deliberations of the four Task Groups. A detailed discussion of each of these items is given in the individual Task Group materials.

The number of problems, approaches, and project areas identified by each Task Group are summarized in Table C-1. The listing which follows provides the corresponding titles for each category, ordered by number. The first digit identifies the problem, the second digit the approach, and the third digit the project area.



Table C-1
DATA SUMMARY FOR LUNG DISEASES PANEL

No.	Problem Area	Approaches	Project Areas
1	The Normal Lung	7	44
2	Environmental Respiratory Diseases	8	28
3	Emphysema and Chronic Bronchitis	15	43
4	Pediatric Obstructive Respiratory Diseases	8	21
5	Allergic Airway Disease-Asthma	9	26
6	Diffuse Interstitial Respiratory Diseases	7	21
7	Infectious Respiratory Diseases	15	52
8	Sarcoid and Granulomatous Lung Diseases	7	15
9	Hypersensitivity Lung Diseases	7	19
10	Pulmonary Vascular Diseases	19	43
11	Hyaline Membrane Disease of the Newborn	10	28
12	Cystic Fibrosis	7	23
13	Acute and Chronic Respiratory Failure	9	29
14	Extra-Pulmonary Manifestations of Respiratory Diseases	7	53
15	Education in Lung Diseases	4	15
TOTAL		139	460

DATA SUMMARY FOR
PROBLEM AREA 1

THE NORMAL LUNG



PROBLEM AREA 1. THE NORMAL LUNG

- 1.1 Approaches to Study of Normal Structure and Function of Lung.
 - 1.1.1 New studies of lung morphology by means of scanning and transmission electron microscopy, freeze-etch, high-voltage electron microscopy, etc., and the relationship of these to lung function.
 - 1.1.2 Morphometry of lung tissues.
 - 1.1.3 Biophysical properties of lung as an organ.
 - 1.1.4 Changes with maturation of the lung ultrastructure.
 - 1.1.5 Mechanical properties of the ventilatory apparatus.
 - 1.1.6 Mechanical properties of the pulmonary vascular bed.
 - 1.1.7 Neurophysiologic regulation of ventilation.
- 1.2 Study of Chemical Structure of Individual Lung Components.
 - 1.2.1 Gross chemical composition.
 - 1.2.2 Connective tissue (collagen, proteoglycans, elastin, reticulin): isolation and characterization.
 - 1.2.3 Alveolar walls: basement membrane, fibrous proteins.
 - 1.2.4 Surface active substances (e.g., surfactant).
 - 1.2.5 Physical properties of individual lung components.
 - 1.2.6 Changes with maturation of lung components.
- 1.3 Study of Normal Cell Biology and Molecular Biology of Uniform Populations of Lung Cells.
 - 1.3.1 Separation of uniform cell populations from the lung.
 - 1.3.2 Growth of diploid, long-term cell lines of uniform type.
 - 1.3.3 Classical subcellular fractionation (mitochondria, lysosomes, etc.) from uniform cells.
 - 1.3.4 Studies of energy metabolism.
 - 1.3.5 Studies of transcription and translation.
 - 1.3.6 Lipid and prostaglandin synthesis.
 - 1.3.7 Responses to pharmacologic agents.
 - 1.3.8 Genetic controls of cell functions.
 - 1.3.9 Changes with maturation of cell functions.
- 1.4 Study of Transport Barriers and Membrane Systems of Lung.
 - 1.4.1 Characterization of transport barriers in terms of irreversible thermodynamics.
 - 1.4.2 Characterization of membrane functions in individual cell lines of the lung.
 - 1.4.3 Determination of effects of physical and chemical agents on above characteristics.
 - 1.4.4 Studies of oxygen transport.
 - 1.4.5 Studies of carbon dioxide transport.
 - 1.4.6 Studies of inert and anesthetic gas exchanges.
 - 1.4.7 Determination of relative roles of convection and diffusion in airways and tissues.
 - 1.4.8 Studies of barrier and membrane systems with growth and maturation.

- 1.5 Study of Respiratory System Mucus Secretions.
 - 1.5.1 Structure, e.g., biochemistry of glycoproteins.
 - 1.5.2 Synthesis of glycoproteins (e.g., activity of golgi enzymes).
 - 1.5.3 Physico-chemical characteristics of glycoprotein and other mucus secretions.
 - 1.5.4 Flow characteristics of respiratory mucin.
 - 1.5.5 Cell biology of mucin assembly and extrusion.
- 1.6 Study of Ciliary Structure and Function of Lung.
 - 1.6.1 Cell biology of ciliated epithelium.
 - 1.6.2 Physiologic controls of ciliary integrity.
 - 1.6.3 Ciliary responses to pharmacologic agents.
- 1.7 Study of Normal Development and Aging of Lung.
 - 1.7.1 Lung embryology and teratology.
 - 1.7.2 Normal development of lung parenchyma.
 - 1.7.3 Developmental abnormalities.
 - 1.7.4 Characteristics of aging lung.
 - 1.7.5 Factors influencing aging in lung.
 - 1.7.6 Normal values for functions of lung with development and aging.

DATA SUMMARY FOR
PROBLEM AREA 2

ENVIRONMENTAL RESPIRATORY DISEASES



PROBLEM AREA 2. ENVIRONMENTAL RESPIRATORY DISEASES

- 2.1 Evaluation of Effect of Smoking Tobacco or Similar Substances on the Lung.
 - 2.1.1 Estimate risk of smoking tobacco or similar substances on respiratory diseases.
 - 2.1.2 Mechanism of damage in smoking.
 - 2.1.3 Possible synergism with other environmental factors.
 - 2.1.4 Effects on pulmonary function and respiratory symptoms.
 - 2.1.5 Identification of factors that lead persons to smoke and how to alter habit.
 - 2.1.6 Effect of reducing tar and/or nicotine—to include effect of filters and inhaling on respiratory functions and symptoms.
 - 2.1.7 Effect of tobacco smoke pollution in public places on nonsmokers.
 - 2.1.8 Pharmacologic substitutes or counteractants.
 - 2.1.9 Study of asymptomatic heavy smokers to identify factors that protect them.
- 2.2 Evaluation of Effect of Various Occupational Exposures.
 - 2.2.1 Mechanism of damage in occupational exposure to particular materials, e.g., silica, chlorine.
 - 2.2.2 Prospective epidemiologic studies of exposed populations.
 - 2.2.3 Deposition and body distribution of particulates and gases.
 - 2.2.4 Interaction of particulates and gases and infectious agents.
- 2.3 Evaluation of Effects of General Air Pollutants.
 - 2.3.1 Long-term studies of various animal species to realistic levels of pollutants.
 - 2.3.2 Prospective studies of random samples of populations at various ages and exposed to different types of pollutants, e.g., oxidizing vs. reducing types.
- 2.4 Evaluation of Effects of Various Physical Factors.
 - 2.4.1 Role of ambient temperature and humidity (including mist and acid rain) in development of respiratory disease.
 - 2.4.2 Role of low PO₂ in development of chronic respiratory disease in man and animals.
 - 2.4.3 Effect of high PO₂ on respiratory structure and function.
 - 2.4.4 Prospective studies of random samples of populations of different ages.
- 2.5 Development of Screening Tests for Early Detection of Lung Disease in Occupational Groups.
 - 2.5.1 Development and evaluation of more sensitive and specific tests for detection of early disease of the lung.
 - 2.5.2 Prospective studies of occupational groups.
- 2.6 Evaluation of Effectiveness of Various Compounds to Prevent Lung Damage or Altered Function.
 - 2.6.1 Effectiveness of polypyridien-N-oxide in control of fibrosis due to silica.
 - 2.6.2 Effectiveness of other compounds in control of fibrosis due to silica.
- 2.7 Evaluation of Various Rehabilitation Regimens.
 - 2.7.1 Role of physical therapy.
 - 2.7.2 Role of occupational therapy.
 - 2.7.3 Role of exercise.

- 2.7.4 Role of psychological support.
- 2.8 Development of Comprehensive Rehabilitation Programs.
 - 2.8.1 Development of model programs.



DATA SUMMARY FOR
PROBLEM AREA 3

EMPHYSEMA AND CHRONIC BRONCHITIS



PROBLEM AREA 3. EMPHYSEMA AND CHRONIC BRONCHITIS

- 3.1 Determination of Pathophysiology.
 - 3.1.1 Study of control of mucus secretion.
 - 3.1.2 Study of defense mechanisms.
 - 3.1.3 Study of response to injury.
 - 3.1.4 Study of relationship of pathology to function.
 - 3.1.5 Study of cell turnover including macrophages, alveolar lining cells, goblet and mucous-secreting cells.
 - 3.1.6 Study of surfactant, specifically turnover rates, mechanism of clearance of surfactant and quantitation of the amount present with regard to age.
 - 3.1.7 Study of distribution of lung parenchymal stresses in response to injury.
 - 3.1.8 Study of intercellular functions.
- 3.2 Determination of Etiologic Factors through Epidemiologic Studies.
 - 3.2.1 Role of infectious agent, i.e., bacterial, fungal, viral or parasitic.
 - 3.2.2 Clarification of role of smoking and air pollution as either direct or adjuvant factor.
 - 3.2.3 Role of genetic factors.
 - 3.2.4 Role of atmospheric, climatic and geographic factors.
- 3.3 Study of Risk Factors.
 - 3.3.1 Study of means to diminish risk factors.
- 3.4 Development of Analytic Models of Lungs.
 - 3.4.1 Development of mechanical, electrical and mathematical models.
- 3.5 Study of Genetic Mechanisms.
 - 3.5.1 Molecular basis of alpha₁-antitrypsin deficiency.
 - 3.5.2 Search for a genetic animal model.
 - 3.5.3 Determination of the susceptibility of individuals with various inheritance patterns of alpha₁-antitrypsin to develop lung disease.
 - 3.5.4 Search for other genetic abnormalities resulting in lung disease.
- 3.6 Study of Mechanisms of Pulmonary Injury.
 - 3.6.1 Identification and characterization of the role of proteolytic substances in lung damage.
 - 3.6.2 Relationship between liver, lung, and other organ dysfunction in alpha₁-antitrypsin deficiency.
 - 3.6.3 Evaluation of the effect of proteolytic enzymes on structural and metabolic features of the lung.
 - 3.6.4 Characterization of other serum and tissue inhibitors of proteolysis.
 - 3.6.5 Development of animal models.
 - 3.6.6 Relationship between alpha₁-antitrypsin deficiency and environmental factors, allergy, infection, respiratory distress syndrome and other diseases.
- 3.7 Development of Means for Early Diagnosis.
 - 3.7.1 Standardization of historical information (i.e., cough, sputum, disability) to improve epidemiologic studies which will eventually aid in early detection.



- 3.7.2 Development of biochemical, immunologic and physiologic techniques to determine presymptomatic disease.
- 3.7.3 Validation of newer tests of pulmonary function.
- 3.7.4 Development of more sensitive diagnostic devices.
- 3.8 Development of Simple and Accurate Diagnostic Tests.
 - 3.8.1 Improvement and simplification of methods for quantitating and phenotyping alpha₁-antitrypsin.
 - 3.8.2 Evaluating the need for measuring alpha₁-antitrypsin in amniotic fluid, cord blood and other body fluids.
- 3.9 Evaluation of Treatment Modalities.
 - 3.9.1 Effects of removal of irritants, i.e., controlled environment such as filtered air, high and low humidity, etc.
 - 3.9.2 Effects of drugs, bronchodilators, antibiotics, etc.
 - 3.9.3 Effects of mechanical devices.
 - 3.9.4 Effects of prolonged oxygen therapy.
- 3.10 Development of Treatment Devices.
 - 3.10.1 Development of more efficacious treatment devices.
- 3.11 Development of Methods for Correcting Alpha₁-Antitrypsin Deficiency.
 - 3.11.1 Use of replacement therapy.
 - 3.11.2 Evaluation of methods for inducing formation and release of alpha₁-antitrypsin from liver.
 - 3.11.3 Tissue transplantation.
- 3.12 Control of Environment.
 - 3.12.1 Effectiveness of avoidance of smoking.
 - 3.12.2 Effectiveness of avoidance of occupational and atmospheric irritants for reducing lung disease in alpha₁-antitrypsin deficient subjects.
 - 3.12.3 Effect of prevention and early treatment of respiratory infections in reducing the progress of lung damage in alpha₁-antitrypsin deficiency.
- 3.13 Evaluation of Therapeutic Approaches.
 - 3.13.1 Evaluation of prophylactic therapy.
 - 3.13.2 Evaluation of natural course of the disease.
- 3.14 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)
- 3.15 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 4

PEDIATRIC OBSTRUCTIVE RESPIRATORY DISEASES

PROBLEM AREA 4 PEDIATRIC OBSTRUCTIVE RESPIRATORY DISEASES

- 4.1 Sharpened Definition of Syndromes.
 - 4.1.1 Epidemiology, including family histories.
 - 4.1.2 Measurement of physiologic derangements.
 - 4.1.3 Documentation of microbiological findings.
 - 4.1.4 Measurement of individual's immune status.
 - 4.1.5 Assessment of radiographic finding.
- 4.2 Prospective Studies of Children.
 - 4.2.1 Exploration susceptibility of infant's lungs to pollutants.
 - 4.2.2 Study of natural course of respiratory diseases in childhood.
- 4.3 Clarification of Infectious Component.
 - 4.3.1 Case etiologic study.
- 4.4 Study of Behavior of Airways as a Function of Size and Age.
 - 4.4.1 Study of pathological specimens for mechanical properties of airways and other abnormalities.
 - 4.4.2 Dimensions of neural regulation airways.
 - 4.4.3 Pharmacologic response of airways.
 - 4.4.4 Reflex patterns between upper and lower airways.
 - 4.4.5 Effects of temperature, humidity, and mist.
- 4.5 Improved Evaluation of Pulmonary Function.
 - 4.5.1 Noninvasive methods to study lung function.
 - 4.5.2 Noninvasive approaches to pulmonary vascular function.
 - 4.5.3 Safer radiologic examination with or without contrast media.
- 4.6 Evaluation of Pharmacologic Agents.
 - 4.6.1 Autonomic drugs.
 - 4.6.2 Oxygen therapy.
 - 4.6.3 Antiinflammatory agents.
 - 4.6.4 Expectorants.
 - 4.6.5 Other bronchodilators.
- 4.7 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)
- 4.8 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 5

ALLERGIC AIRWAY DISEASE -- ASTHMA



PROBLEM AREA 5. ALLERGIC AIRWAY DISEASE – ASTHMA

- 5.1 Determination of Etiology and Pathophysiology.
 - 5.1.1 Genetic studies in families, twins and animals.
 - 5.1.2 Chemical mediators of airway reactivity should be studied concerning their mode of action, their receptors, and means of blocking these.
 - 5.1.3 Identification of immunologic reaction patterns.
 - 5.1.4 Determination of constitutional differences in pharmacologic reactivity.
 - 5.1.5 Study of mucociliary transport.
 - 5.1.6 Characterization of properties of abnormal mucus.
 - 5.1.7 Development of animal models.
 - 5.1.8 Function of mast cells.
 - 5.1.9 Role of lymphocyte and adenylyclase.
 - 5.1.10 Role of the eosinophil.
- 5.2 Determination of Patterns of Incidence.
 - 5.2.1 In family pedigrees at high and low risk for atopic diseases.
 - 5.2.2 Relation to causative agents such as castor bean or bacterial enzymes.
 - 5.2.3 Relation of asthma to respiratory infections.
 - 5.2.4 Longitudinal studies of natural history.
- 5.3 Development of Simple, Accurate Means of Diagnosis.
 - 5.3.1 Pulmonary function and response to bronchodilators.
 - 5.3.2 Methacholine inhalation challenge test.
 - 5.3.3 Sputum examination for eosinophils.
 - 5.3.4 Identify the atopic abnormality by skin tests and in vitro studies of reagin.
- 5.4 Avoidance of Allergens and Irritants in Environment.
 - 5.4.1 Recognition of offending agents.
- 5.5 Development of Pharmacologic Agents.
 - 5.5.1 Development of more selective bronchodilators.
 - 5.5.2 Development of mucolytic agents.
 - 5.5.3 Development of mediator antagonists.
- 5.6 Evaluation of Immunologic Agents.
 - 5.6.1 Evaluation of immunologic aspects including hyposensitization.
 - 5.6.2 Evaluation of corticosteroids and agents that inhibit release of mediators in association with antigen-antibody reaction.
- 5.7 Status Asthmaticus.
 - 5.7.1 Evaluation of current methods.
 - 5.7.2 Development and demonstration of optimal methods.
- 5.8 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)

5.9 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)



DATA SUMMARY FOR
PROBLEM AREA 6

DIFFUSE INTERSTITIAL RESPIRATORY DISEASES



PROBLEM AREA 6 DIFFUSE INTERSTITIAL RESPIRATORY DISEASES

6.1 Determination of Pathophysiology.

- 6.1.1 Study relationship of structure and function.
- 6.1.2 Study the relationship of biochemical function and alterations in metabolism of phospholipids, proteins, collagen, glycoproteins, etc., to pathologic and physiologic changes.
- 6.1.3 Determine physiologic changes in various entities and relate to above mentioned studies.
- 6.1.4 Study deviation from normal defense mechanisms in the disease entities and in animal models.
- 6.1.5 Determine response to injury in animal model and follow longitudinally to determine the evolution of pathologic changes.

6.2 Determination of Causative Factors.

- 6.2.1 Epidemiologic studies to determine host factors, environmental factors, and other related elements that might be common to a group or a single interstitial disease.
- 6.2.2 Study genetic variations in response to lung injury by various agents.
- 6.2.3 Study relationships between interstitial diseases, such as rheumatoid lung, lupuserythematosus lung, changes in scleredema or other groups of diseases which have similar pathology.
- 6.2.4 Study the role of viral infections.
- 6.2.5 Study of relationship of drugs, first by identifying carefully in an epidemiologic study all drug ingestion in patients with known disease and study intensively drugs that are known to cause interstitial disease such as hydralazine, busulfan and hexamethonium.
- 6.2.6 Study relationship of radiation to development of fibrosis.

6.3 Study of Means to Diminish Risk Factors.

- 6.3.1 Study the effects of diminished environmental factors by use of filtered air, masks, etc.
- 6.3.2 Study the effects of modifying a nonpulmonary disease, such as rheumatoid arthritis or other collagen disease on the pulmonary manifestations.
- 6.3.3 Identify other risk factors including allergic and altered immune responses.

6.4 Development of Means of Early Detection and Diagnosis.

- 6.4.1 Development of new methods for obtaining and interpreting chest roentgenograms.
- 6.4.2 Improved biopsy techniques: lung, pleura and mucosa.
- 6.4.3 Improved immunologic studies of the patient and biopsy material regarding cell-mediated immunity autoantigens, competence of lymphocytes and localization of immunoproteins in pathologic specimen.

6.5 Evaluation of Treatment Modalities.

- 6.5.1 Role of corticosteroids in studies in humans and in animal models.
- 6.5.2 Clinical traits of promising pharmacologic agents.
- 6.5.3 Evaluation of immunosuppressive therapy in controlled studies.
- 6.5.4 Evaluation of antifibrogenic compounds utilizing animal model.

- 6.6 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)
- 6.7 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 7

INFECTIOUS RESPIRATORY DISEASES

PROBLEM AREA 7. INFECTIOUS RESPIRATORY DISEASES

- 7.1 Study of Lung Defense Mechanisms.**
 - 7.1.1 Mucociliary transport.
 - 7.1.2 Characterization of properties of abnormal mucus.
 - 7.1.3 Lymphatic pathways.
 - 7.1.4 Lung phagocytes in defense mechanisms.
 - 7.1.5 Local and circulating immunoglobulins.
 - 7.1.6 Studies of cellular immunity to infectious agents.
 - 7.1.7 Surfactant's role in bacteriostasis.
 - 7.1.8 Interaction of environmental factors.
 - 7.1.9 Determinants of inflammatory reactions, e.g., varying reactions of lung tissue to differing infectious agents.
 - 7.1.10 Ontogeny of lung defense mechanisms.
- 7.2 Study of Host Factors that Modify Infection.**
 - 7.2.1 Epidemiological studies to determine patient characteristics associated with high incidence of infection.
 - 7.2.2 Interaction of host factors, occupational exposure and infection.
 - 7.2.3 Interaction of host factors, atmospheric exposure and infection.
 - 7.2.4 Determination of host factors allowing colonization of ill patients with unusual infectious agents, e.g., immune deficits.
- 7.3 Interaction of Upper and Lower Respiratory Tract Defense Mechanisms.**
 - 7.3.1 Relationship of colonization of upper and lower respiratory tracts.
 - 7.3.2 Regional variation in immunological relations.
 - 7.3.3 Cell adherence of infectious agents.
 - 7.3.4 Interrelation of clearance routes.
- 7.4 Development of Simple, Accurate Means of Diagnosis.**
 - 7.4.1 Serological tests.
 - 7.4.2 Differentiation of colonization from infection.
 - 7.4.3 Rapid diagnosis mechanisms, e.g., immunofluorescence, negative staining for electron microscopy.
- 7.5 Determination of Magnitude of Fungal Diseases.**
 - 7.5.1 Development of mandatory case reporting systems.
 - 7.5.2 Growth characteristics of fungi which allow human colonization.
- 7.6 Determination of Magnitude of Nonbacterial, Nonviral Diseases.**
 - 7.6.1 Development of mandatory case reporting systems.
 - 7.6.2 Growth characteristics of pneumocystis carinii, etc., which allow colonization and disease.
- 7.7 Continued Definition of Etiology of Respiratory Syndromes in Children.**
 - 7.7.1 Refinements in current technology utilized to define bacterial, viral and mycoplasmal infections or colonization.

- 7.7.2 Application of newer modalities such as organ culture, cocultivation, radio-immunoassay of antibody, etc., to these diseases.
- 7.7.3 Development of methods for determining why different viral agents localize in different sites of the airways.
- 7.7.4 Determination of the role of maternal antibody in the infant.
- 7.8 Development of Means for Early Recognition of Immunodeficiency.
 - 7.8.1 Development of screening services for study of cord blood lymphocyte and phagocytic functions.
 - 7.8.2 Development of uniform screening tests and antigens for assessment of cellular immune function.
 - 7.8.3 Development of newer and more sensitive methods for detecting immunodeficiency.
- 7.9 Immunoprophylaxis Development.
 - 7.9.1 Vaccines, e.g., pneumococcal, influenzal.
 - 7.9.2 Purified immunogenic components of tuberculosis vaccines.
- 7.10 Chemotherapy Development.
 - 7.10.1 Antiviral agents.
 - 7.10.2 Determination of shortest possible treatment regimen for tuberculosis.
 - 7.10.3 More effective antifungal agents.
 - 7.10.4 Antimicrobials for resistant bacteria.
- 7.11 Studies in Immunologic Reconstitution.
 - 7.11.1 Development of *in vitro* models for the study of immunologic enhancement.
 - 7.11.2 Characterization of enhancing antibodies or factors.
 - 7.11.3 Study of conditions favoring development of enhancing antibodies.
 - 7.11.4 Comparative study of HL-A and MLR responsiveness in immunodeficiency families.
 - 7.11.5 Evaluation of immunocompetent cells from different sources in restoring immunocompetence.
 - 7.11.6 Biochemical and biological characterization of transfer factor.
 - 7.11.7 Evaluation of transfer factor therapy in immunodeficiency.
- 7.12 Application of Germ-Free Units in the Management of Immunodeficiency.
 - 7.12.1 Studies directed to the practical use of isolated germ-free units in the treatment of immune deficient patients. These should be combined with studies of the biology of the immune deficient state.
 - 7.12.2 Study of the psychosocial effects of germ-free isolation on immunodeficiency patients.
 - 7.12.3 Microbiological monitoring of the effectiveness of various germ-free isolation units.
 - 7.12.4 Study of morbidity and mortality rates in severe combined immunodeficiency patients maintained in germ-free isolation units.
- 7.13 Study of Replacement Therapy in Immunodeficiency.
 - 7.13.1 Development of more efficient and effective ways of preparing gamma globulin suitable for intravenous infusion.
 - 7.13.2 Evaluation of the safety and efficacy of plasma therapy in immunodeficiency through use of a single donor.

7.13.3 Development of hepatitis antigen-free plasma banks for therapy of immunodeficiency.

7.14 Evaluation of Various Rehabilitation Regimens.

(See Problem Area 2, Approach 2.7.)

7.15 Development of Models of Comprehensive Rehabilitation Programs.

(See Problem Area 2, Approach 2.8.)



DATA SUMMARY FOR
PROBLEM AREA 8

SARCOID AND GRANULOMATOUS LUNG DISEASES



PROBLEM AREA 8 SARCROID AND GRANULOMATOUS LUNG DISEASES

- 8.1 Determination of Incidence and Pathogenesis.
 - 8.1.1 Role of genetic factors.
 - 8.1.2 Role of dietary factors.
 - 8.1.3 Role of environmental factors.
 - 8.1.4 Antecedent "triggering" diseases (infections, environmental, etc.).
 - 8.1.5 Variation in antibody responses to immunization.
 - 8.1.6 Underlying (preexisting) alterations in delayed type hypersensitivity.
 - 8.1.7 Mechanism of foreign body reaction to varied immunologic states.
- 8.2 Determination of Pathophysiology.
 - 8.2.1 Development of animal models.
- 8.3 Improved Detection and Diagnosis.
 - 8.3.1 Establish the role of the Kveim test in the diagnosis of sarcoid.
 - 8.3.2 Development of new means of early detection.
- 8.4 Evaluation of Treatment Modalities.
 - 8.4.1 Efficacy of transfer factor.
 - 8.4.2 Efficacy of immunosuppressive drugs.
 - 8.4.3 Efficacy of corticosteroids.
 - 8.4.4 Long-term controlled clinical studies.
- 8.5 Development of Therapy.
 - 8.5.1 Development of new modalities.
- 8.6 Evaluation of Various Rehabilitation Regimens.

(See Problem Area 2, Approach 2.7.)
- 8.7 Development of Models of Comprehensive Rehabilitation Programs.

(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 9

HYPERSENSITIVITY LUNG DISEASES



PROBLEM AREA 9. HYPERSENSITIVITY LUNG DISEASES

- 9.1 Determination of Pathophysiology.
 - 9.1.1 Development of animal models.
 - 9.1.2 Study of mechanisms by which inhaled antigens produce an immunogenic response.
 - 9.1.3 Study of humoral and cellular mechanisms in the production of the pulmonary lesions.
 - 9.1.4 Pulmonary function studies.
- 9.2 Determination of Incidence and Etiology.
 - 9.2.1 Identification of antigens by screening suspected dusts.
 - 9.2.2 Close observation and pulmonary function studies when re-exposed to the suspected environment.
 - 9.2.3 Provocative inhalation challenge.
 - 9.2.4 Development of more sensitive techniques such as counter-immunoelectrophoresis to identify antibodies.
 - 9.2.5 Longitudinal studies of natural history.
- 9.3 Development of Simple, Accurate Means of Diagnosis.
 - 9.3.1 Standardization and commercial availability of antigen sources.
 - 9.3.2 Clinical availability of specific and sensitive immunological tests of serum and respiratory secretions.
 - 9.3.3 Evaluation of skin testing with antigens.
 - 9.3.4 Close observation of patient when reexposed to the suspected environment.
 - 9.3.5 Pulmonary function studies.
- 9.4 Development of Pharmacologic Agents.
 - 9.4.1 Development of specific antiinflammatory agents.
 - 9.4.2 Treatment with corticosteroids.
 - 9.4.3 Development of other agents.
- 9.5 Avoidance of Antigens.
 - 9.5.1 Recognition of host's immunologic response to inhalation of organic dusts.
 - 9.5.2 Recognition and avoidance of disease-producing organic dusts and other sources.
- 9.6 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)
- 9.7 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 10

PULMONARY VASCULAR DISEASES



PROBLEM AREA 10. PULMONARY VASCULAR DISEASES

- 10.1 Study of Abnormal Cardiopulmonary Function.
 - 10.1.1 Effects of long- and short-term graded increases of pulmonary artery pressure.
 - 10.1.2 Pathogenesis of pulmonary and vascular disorders resulting in cor pulmonale. See also Problem Area 3.
 - 10.1.3 Biochemical and metabolic changes.
 - 10.1.4 Physiologic changes in hemodynamics and smooth muscle function.
- 10.2 Determination of Pathophysiology and Pathogenesis of Pulmonary Hypertension.
 - 10.2.1 Neural effects.
 - 10.2.2 Endocrine effects.
 - 10.2.3 Electrolyte and metabolic effects.
- 10.3 Determination of Pathogenesis of Pulmonary Edema.
 - 10.3.1 Water content of lung and its compartmental distribution.
 - 10.3.2 Metabolic activities of normal and edematous lungs.
 - 10.3.3 Defense mechanisms of edematous lungs.
 - 10.3.4 Characterization of endothelial and epithelial barriers in terms of irreversible thermodynamics.
 - 10.3.5 Effects of various agents on barrier characteristics.
 - 10.3.6 Role of lymphatics.
 - 10.3.7 Role of surfactant.
 - 10.3.8 Removal of lung liquid at birth.
 - 10.3.9 Composition of alveolar fluid.
- 10.4 Study of Structural Changes in Pulmonary Edema.
 - 10.4.1 Correlation of functional and structural changes in pulmonary edema.
- 10.5 Study of Contributing Factors to Pulmonary Edema.
 - 10.5.1 Clinical situations of pulmonary edema.
 - 10.5.2 Associated disorders of pulmonary edema.
- 10.6 Identification and Study of Extrinsic Factors Affecting Pulmonary and Vascular Dysfunction.
 - 10.6.1 Environmental pollution; agents specifically related to pulmonary damage; mechanisms of action.
- 10.7 Reduction or Suppression of Agents and Factors Associated with Respiratory Damage.
 - 10.7.1 Instrumentation to detect and identify agents and factors associated with respiratory damage.
- 10.8 Determination of Incidence and Etiology.
 - 10.8.1 Prospective epidemiologic studies of cor pulmonale.
 - 10.8.2 Prospective epidemiologic studies of pulmonary hypertension.
 - 10.8.3 Prospective epidemiologic studies of pulmonary edema.
- 10.9 Development of Techniques and Devices for Simple, Accurate Diagnosis of Cardiac Abnormalities.
 - 10.9.1 Catheterization techniques for flow-pressure relationships.

- 10.9.2 Objective detection and quantification of right ventricular hypertrophy.
- 10.9.3 Noninvasive techniques for estimation of pressure and of right ventricular hypertrophy.
- 10.10 Development of Techniques and Devices for Simple, Accurate Diagnosis of Pulmonary Abnormalities.
 - 10.10.1 Single breath testing of respiratory functions with minimal patient or subject cooperation.
 - 10.10.2 Determine usefulness of immunologic and related studies as diagnostic aids.
- 10.11 Conduct of Clinical Studies.
 - 10.11.1 Clinical screening studies.
- 10.12 Techniques and Devices to Determine Presence and Extent of Pulmonary Edema.
 - 10.12.1 Indicator dilution techniques.
 - 10.12.2 Radiant energy absorption and other procedures (ultrasound, hologram, radiographic technique, capacitance changes).
- 10.13 Development of Animal and In Vitro Models.
 - 10.13.1 Development of animal models.
 - 10.13.2 Development of isolated perfused lung preparation.
- 10.14 Evaluation of Treatment Modalities.
 - 10.14.1 Comparison of effectiveness of different therapeutic approaches.
- 10.15 Study of Roles of Associated Factors in Treatment.
 - 10.15.1 Environmental pollution control.
 - 10.15.2 Role of drugs and other pharmacologic agents.
- 10.16 Efficacy of Various Procedures and Therapies in Different Clinical Situations of Pulmonary Edema.
 - 10.16.1 Effects of decreased venous return.
 - 10.16.2 Effects of vasoactive and cardioactive drugs.
 - 10.16.3 Effects of various types of controlled respiration and of oxygen.
 - 10.16.4 Development of new therapeutic agents (Dextran, prostaglandins).
- 10.17 Development of Life-Support Mechanisms for Patients with Severe Cor Pulmonale (See also Problem Area 14).
 - 10.17.1 Extracorporeal oxygenators.
 - 10.17.2 Various means of extrapulmonary oxygen administration.
- 10.18 Evaluation of Various Rehabilitation Regimens.
 - (See Problem Area 2, Approach 2.7.)
- 10.19 Development of Models of Comprehensive Rehabilitation Programs.
 - (See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 11

HYALINE MEMBRANE DISEASE OF THE NEWBORN



PROBLEM AREA 11. HYALINE MEMBRANE DISEASE OF THE NEWBORN

- 11.1 Definition of Population at Risk.
 - 11.1.1 Epidemiologic studies.
 - 11.1.2 Effects of obstetric measures.
 - 11.1.3 Role of other maternal illnesses.
 - 11.1.4 Possible genetic basis.
- 11.2 Prenatal Diagnosis.
 - 11.2.1 Studies of amniotic fluid.
- 11.3 Evaluation of Methods to Prevent Premature Birth .
 - 11.3.1 Maternal factors that predispose to prematurity.
 - 11.3.2 Mechanism of onset of labor.
- 11.4 Evaluation of Supportive Measures in the Early Neonatal Period.
 - 11.4.1 Role of fetal and neonatal blood volume, significance of and deviations in vascular pressures.
 - 11.4.2 Importance of effective resuscitation.
- 11.5 Study of Post Mortem Material and Animal Models.
 - 11.5.1 Morphometry of immature diseased lung.
 - 11.5.2 Biochemical abnormalities in lipids and proteins extracted from lungs.
 - 11.5.3 Ultrastructural changes and histochemical events in alveolar cells and capillaries.
 - 11.5.4 Biochemical events in developing primate lungs, especially pathways of lipid synthesis.
 - 11.5.5 Relationship of interventricular hemorrhage to lung disease.
 - 11.5.6 Ways in which immature lung repairs itself.
- 11.6 Improvement of Tools for Early Diagnosis.
 - 11.6.1 Evaluation of cord blood proteins and enzymes as predictors of disease.
 - 11.6.2 Search for new indicators of likelihood of disease in maternal blood, amniotic fluid and urine.
- 11.7 Establishment of Criteria for Optimal Care.
 - 11.7.1 Standardized clinical and pathological definitions.
 - 11.7.2 Evaluation of the best means of transport of infants.
 - 11.7.3 Evaluation of means to accelerate lung maturation.
 - 11.7.4 Evaluation of pharmacologic agents.
 - 11.7.5 Improved methods of assisted respiratory support.
 - 11.7.6 Evaluation of blood oxygenators.
 - 11.7.7 Effects of alterations in blood volume on course of disease.
 - 11.7.8 Role of increasing 2,3 DPG levels in red cells.
- 11.8 Evaluation of Fate of Survivors.
 - 11.8.1 Follow-up clinics to evaluate pulmonary and cerebral function for 10-15 years after the disease.

- 11.8.2 Study of incidence of late sequelae in light of prenatal and neonatal management.
- 11.8.3 Follow-up of immune status of survivors.
- 11.9 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)
- 11.10 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 12

CYSTIC FIBROSIS

PROBLEM AREA 12. CYSTIC FIBROSIS

- 12.1 Study of Biochemistry of Cystic Fibrosis.
 - 12.1.1 Ciliary dyskinetic factor(s) of serum and saliva.
 - 12.1.2 Factor(s) affecting membrane function.
 - 12.1.3 Pathophysiology of exocrine glands.
 - 12.1.4 In vitro analysis of skin fibroblasts.
 - 12.1.5 In vitro tracheobronchial tissue explants.
 - 12.1.6 Studies of cultured leucocytes.
- 12.2 Study of Lung Defense Mechanisms in Cystic Fibrosis.
 - 12.2.1 Mucociliary clearance.
 - 12.2.2 Role of the alveolar macrophage.
 - 12.2.3 Immunologic defenses against infection.
 - 12.2.4 Incidence of immediate hypersensitivity reactions.
 - 12.2.5 Role of pulmonary perfusion and lymphatic drainage.
 - 12.2.6 Environmental influences.
 - 12.2.7 Role played by lower respiratory infections.
 - 12.2.8 Effects on the normal humidification of inspired air in the nose, throat, trachea and major bronchi.
 - 12.2.9 Host factors resulting in increased susceptibility to bacterial infection.
- 12.3 Incidence of Cystic Fibrosis.
 - 12.3.1 Prospective epidemiologic studies.
- 12.4 Development of Techniques for Detection of the Gene.
 - 12.4.1 Methods for prenatal diagnosis.
 - 12.4.2 Methods for identifying the heterozygote and genetic counseling.
 - 12.4.3 Development of animal models.
- 12.5 Development of Therapeutic Measures and Programs.
 - 12.5.1 Prevention by therapeutic abortion of fetus diagnosed as homozygote in fetero.
 - 12.5.2 Determination of natural course of cystic fibrosis.
 - 12.5.3 Development of therapy at the molecular levels.
 - 12.5.4 Evaluation and improvement of present therapeutic methods for long involvement.
- 12.6 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)
- 12.7 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 13

ACUTE AND CHRONIC RESPIRATORY FAILURE



PROBLEM AREA 13 ACUTE AND CHRONIC RESPIRATORY FAILURE

- 13.1 Evaluation of the Natural History of Chronic and Acute Respiratory Disease.
 - 13.1.1 Long-term assessment of patients following respiratory failure, including respiratory distress syndromes.
 - 13.1.2 Longitudinal studies of patients with chronic respiratory diseases.
 - 13.1.3 Reversibility of airways disease.
 - 13.1.4 Coding system for respiratory distress syndrome and acute respiratory failure.
- 13.2 Determination of Mechanisms of Lung Injury.
 - 13.2.1 Defense mechanisms against injury and infection.
 - 13.2.2 Mechanisms and effects of edema formation in the lung.
- 13.3 Development of Means for Earlier Detection of Respiratory Distress Syndromes.
 - 13.3.1 Improved methods of monitoring blood oxygen.
 - 13.3.2 Techniques for determining lung water.
 - 13.3.3 Assess sequential appearance of other physiological parameters.
- 13.4 Early Detection of Respiratory Failure.
(See Problem Area 3, Approach 3.7.)
- 13.5 Evaluation of Treatment Modalities.
 - 13.5.1 Corticosteroids.
 - 13.5.2 Bronchodilators and other pharmacologic compounds.
 - 13.5.3 Digitalis and diuretics.
 - 13.5.4 Antimicrobials.
 - 13.5.5 Mucolytic aerosols.
 - 13.5.6 Humidifying aerosols.
 - 13.5.7 Oxygen therapy.
 - 13.5.8 Removal of irritants.
 - 13.5.9 Mechanical ventilators.
 - 13.5.10 Membrane oxygenators.
 - 13.5.11 Development of new modalities.
- 13.6 Development of Community Emergency Services.
 - 13.6.1 Evaluation of present emergency facilities (emergency rooms, respiratory care units).
 - 13.6.2 Evaluation of present treatment of respiratory care emergencies.
 - 13.6.3 Development of respiratory emergency care equipment.
 - 13.6.4 Development of respiratory emergency care allied manpower.
 - 13.6.5 Development of model respiratory emergency community services (high-density populations, outlying communities, emergency vehicles, etc.).
- 13.7 Study of Repair Mechanisms of the Lung.
 - 13.7.1 Long-term assessment of patients recovering from respiratory distress.
 - 13.7.2 Collagen and other connective tissue metabolism.
 - 13.7.3 Alteration in morphology and function of lung cells as repairs proceed.

- 13.7.4 Genetic and immunologic factors of survivors of respiratory distress syndrome.
- 13.8 Evaluation of Various Rehabilitation Regimens.
(See Problem Area 2, Approach 2.7.)
- 13.9 Development of Models of Comprehensive Rehabilitation Programs.
(See Problem Area 2, Approach 2.8.)

DATA SUMMARY FOR
PROBLEM AREA 14

EXTRA-PULMONARY MANIFESTATIONS OF RESPIRATORY DISEASES

PROBLEM AREA 14. EXTRA-PULMONARY MANIFESTATIONS OF RESPIRATORY DISEASES

- 14.1 Brain Effects of Hypoxia/Hypercapnia/Acidosis.**
 - 14.1.1 Adverse effects of ventilatory therapy in lung disease on cerebral circulation, metabolism and function.
 - 14.1.2 Adjustments of cerebral circulation and CSF/ECF to abnormal blood gases.
 - 14.1.3 Mechanism of brain dysfunction during hypoxia.
 - 14.1.4 Mechanisms and treatment of brain edema in chronic lung disease.
 - 14.1.5 Mechanism and prevention of CO₂ narcosis produced by oxygen therapy.
 - 14.1.6 Pharmacologic agents used in lung disease—effects on brain.
 - 14.1.7 Brain ECF acid-base balance and its alteration by lung disease and its therapy.
 - 14.1.8 Contribution of chronic lung disease to the brain dysfunction of the aged.
- 14.2 Laboratory Studies on the Influence of Hypoxia/Hypercapnia/Acidosis on Growth and Development of Newborn.**
 - 14.2.1 Placental function.
 - 14.2.2 Placental development.
 - 14.2.3 Enzymatic and cellular changes in fetus.
 - 14.2.4 Adaptive changes in acute/chronic exposures of hypoxia/hypercapnia/acidosis.
 - 14.2.5 Does type of acidosis—(metabolic or respiratory)—have different effects?
 - 14.2.6 Role of hypoxia/hypercapnia/acidosis in genesis of abnormalities—hyaline membrane disease, etc.
- 14.3 Epidemiologic Studies on Selected Populations.**
 - 14.3.1 Study of fetal wastage (can compare long-term residents vs. newcomers vs. sea-level dwellers) matched socio-economically and maternal age.
 - 14.3.2 Incidence of fetal abnormalities.
 - 14.3.3 Neonatal mortality—causes.
 - 14.3.4 Growth and development over early years of life.
 - 14.3.5 What are adaptive changes that permit long-term residents at altitudes to produce viable offsprings?
- 14.4 Cellular Biochemical Abnormalities Produced by Hypoxia/Hypercapnia/Acidosis.**
 - 14.4.1 Improvement of techniques of in vivo and in vitro determinations.
 - 14.4.2 Evaluation of morphological and membrane alterations.
 - 14.4.3 Changes in steady state fluxes in response to low oxygen tension.
 - 14.4.4 Assessment of intracellular milieu in acute and chronic alteration.
 - 14.4.5 Determination of abnormal levels of cellular constituents.
 - 14.4.6 Causes of cell death and degeneration.
 - 14.4.7 Biochemical relations in cellular adaptation.
 - 14.4.8 Primary versus second order effects.
 - 14.4.9 Effectiveness of pharmacologic agents on cellular metabolism.

- 14.4.10 Patterns of enzyme adaptation in response to hypoxia/hypercapnia/acidosis.
- 14.4.11 Cellular ionic regulation.
- 14.4.12 Effects on metabolism of changes in intracellular and extracellular pH.
- 14.5 Humoral Agents and Lung Disease.
 - 14.5.1 Biosynthesis and release of bioactive agents.
 - 14.5.2 Metabolism of agents.
 - 14.5.3 Pharmacologic agents.
 - 14.5.4 Biotransformation of exogenous compounds by the lung.
- 14.6 Biochemical Aspects of Tissue Metabolism in High-Altitude Dwellers.
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 - 14.6.4 Pharmacologic responses in high-altitude dwellers.
 - 14.6.5 Genetic factors in response to high-altitude hypoxia.
 - 14.6.6 Enzyme adaptation in high-altitude dwellers.
 - 14.6.7 Cellular chemical changes in response to high altitudes.
- 14.7 Treatment of Hypoxia.
 - 14.7.1 Identify the changes in pulmonary structure and function produced by high O₂ inhalation.
 - 14.7.2 Instrumentation for monitoring changes in lung function during O₂ inhalation.
 - 14.7.3 Studies of the effect of high O₂ inhalation on other organs in addition to the lung.
 - 14.7.4 Investigation of potential agents and approaches to reverse pulmonary O₂ lesions.
 - 14.7.5 Investigation of potential agents and approaches to reverse O₂ lesions in other than the lung.
 - 14.7.6 Development of agents and approaches to augment blood O₂ transport during hypoxemia.
 - 14.7.7 Augmentation of enzymatic support of anaerobic glycolysis to improve energy supply during hypoxia.
 - 14.7.8 Augmentation of enzymatic support of oxidative phosphorylation to improve efficiency of O₂ utilization.
 - 14.7.9 Development of agents and approaches to reverse abnormal redoxstates.
 - 14.7.10 Tailoring tissue-metabolic needs and tissue responses to decreased O₂ supply.
 - 14.7.11 Development of nongaseous forms of systemic O₂ administration.

DATA SUMMARY FOR
PROBLEM AREA 15

EDUCATION IN LUNG DISEASES



PROBLEM AREA 15. EDUCATION IN LUNG DISEASES

15.1 Educatees in Lung Diseases.

- 15.1.1 Evaluation of, and programs for, postgraduate medical education.
- 15.1.2 Evaluation of, and programs for, fellows and trainees in respiratory medicine.
- 15.1.3 Evaluation of, and programs for, education of undergraduate medical students and house staff.
- 15.1.4 Evaluation of, and programs for, postgraduate education of allied health professionals.
- 15.1.5 Evaluation of, and programs for, education of allied health professional students.
- 15.1.6 Evaluation of, and programs for, education of the public.

15.2 Educators in Lung Diseases.

- 15.2.1 Evaluation of, and programs for, educators in physician-scientist training programs.
- 15.2.2 Evaluation of, and programs for, educators in physician-training programs (undergraduate, graduate, and postgraduate).
- 15.2.3 Evaluation of, and programs for, educators in public health schools.
- 15.2.4 Evaluation of, and programs for, educators in allied health professional schools.
- 15.2.5 Evaluation of, and programs for, expert personnel (communications media, public education, psychology, etc.) in public education.

15.3 Educational Curricula in Lung Diseases.

- 15.3.1 Development of innovative, varied, and flexible courses of instruction.
- 15.3.2 Development of innovative and efficacious modes of presenting material through use of such vehicles as television, programmed instruction, computers, and demonstrations.

15.4 Educational Administration in Lung Diseases.

- 15.4.1 Development of planning for, and implementation of, educational administration dealing with medical and allied health professional education.
- 15.4.2 Development of planning for, and implementation of, educational administration dealing with public education.



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NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME IV PANEL REPORTS

PART III

REPORT OF THE BLOOD DISEASES PANEL



APRIL 6, 1973

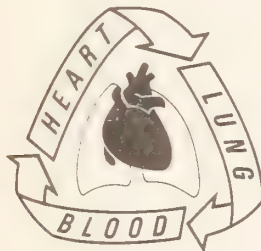
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F O R E W O R D

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423) requires that the National Heart and Lung Institute develop a plan for a National Heart, Blood Vessel, Lung and Blood Disease Program. The Institute established a committee of four panels to assist in the development of program plans for each of the four major program areas:

- Heart and Blood Vessel Diseases
- Lung Diseases
- Blood Diseases
- Blood Resources.

This report was prepared by the Blood Diseases Panel.



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APPENDIX C - DATA SUMMARY



In September 1972, a Panel of 13 physicians and research scientists was appointed to assist in the preparation of a National Plan for a coordinated and accelerated attack on blood disease problems. Seven Task Groups were constituted by this Panel to address specific problem areas in Blood Diseases and each was chaired by a member of the Panel. The topics assigned to the seven Task Groups were:

- Hemophilia and Other Bleeding Disorders
- Disorders of Hemostasis Due to Platelet Abnormalities
- Microcirculatory Thrombosis
- Thromboembolism in Relation to Prosthetic Devices
- Venous Thrombosis and Pulmonary Embolism
- Arterial Thromboembolism
- Hemoglobinopathies.

Some 98 nongovernmentally affiliated doctors of medicine and scientists from 24 states and all regions of the continental United States participated in these seven Task Groups. A series of 10 intensive two-day planning sessions was held during October and November to assess the current state of knowledge and to develop approaches to specific blood disease problems. As a component of the Panel, each Task Group contributed a narrative discussion of its area together with a



series of scientific summaries of proposed project areas. The combined narratives of all the Task Groups exceeded 300 pages, and 391 individual project areas were specified (see Appendix C). The Panel has distilled this volume of material and discusses herein, as its report, the conclusions reached by the seven Task Groups, as well as its own specific program recommendations.

This report is divided into three major sections:

- Part II - The Problems and Proposed Programs
- Part III - Summary of Panel Recommendations
- Part IV - The Legislation and the Proposed Program.

Part I presents a discussion of the current state of knowledge in each problem area and a set of comprehensive recommendations which are developed in terms of the four major program objectives: prevention, detection and diagnosis, treatment and management, and rehabilitation. The major problems identified by the Task Groups are discussed in Part II in nine major topics under two broad subject headings:

- Thrombosis and Hemorrhage
 - The Hemophilias
 - Platelets
 - Microcirculation
 - Vascular Prostheses
 - Arterial and Venous Thromboembolism



- The Hemoglobinopathies (Hereditary Red Cell Disorders)

- Sickle Cell Disease and Sickle Cell Trait
- Hemoglobin Variants Other than Hemoglobin S
- Thalassemia
- Red Cell Enzymes and Red Cell Membranes.

The comprehensive sets of recommendations developed in Part II are aggregated to a degree and are presented in Part III as an overall summary of Panel recommendations under five broad categories of proposed program efforts:

- Establishment of "Demonstration" Centers
- Establishment of Comprehensive "Registries"
- Development of New Technology
- Implementation of Multicenter Clinical Trails
- Pursuit of Fundamental Knowledge.

As a second important section of Part III, the full comprehensive sets of recommendations are presented in tabular form on the basis of suggested priorities. In Part IV, the recommendations are correlated with the legislative requirements as set forth in the National Heart, Blood Vessel, Lung and Blood Act of 1972.



PART I

INTRODUCTION



PART I
INTRODUCTION

1.1 MAGNITUDE OF THE PROBLEM

The national impact of the diseases assigned to the Blood Diseases Panel is imposing. Arterial thrombosis, in conjunction with atherosclerosis, is an important contributor to acute myocardial infarction, the number one cause of death in the United States; and arterial thrombosis and cerebral hemorrhage play major roles in stroke, which is the number three cause of death. Thrombosis frequently is the final occlusive episode in these diseases leading to infarction. Moreover, atherosclerosis without thrombosis would be a much less serious pathological process. Thromboembolic episodes occur in relation to cardiac valves diseased by rheumatic fever and atherosclerosis, as well as with their prosthetic replacements. In addition, thrombosis and embolism are associated with cardiac arrhythmias, congestive heart failure, and intimal damage in the carotid area, the aortoiliac region, and the arteries of the lower extremities.



Large aneurysms, whether of the myocardium or the peripheral vessels, cardiovascular collapse from any cause, certain types of gastrointestinal malfunction and bowel necrosis, gangrene of the extremities, some infections, and severe blood dyscrasias may also be associated with arterial thrombosis. Finally, thrombosis involving the arteries, veins, or microcirculatory apparatus of the kidney contributes to renal failure, which is the number four cause of death in this country.

Venous thrombosis and pulmonary embolism are also major health hazards. It has been estimated that about 300,000 patients are hospitalized annually in the United States with pulmonary embolism and that more than 50,000 of these patients die. The cost of hospitalization of the 250,000 survivors approximates \$750 million per year. These figures do not include the morbidity and cost of patients with venous thrombosis alone or the substantial cost of the long-term outpatient management which such patients usually require. Available data indicate that venous thromboembolism is the most common nonsurgical cause of death in patients hospitalized for orthopedic procedures, the most frequent nonobstetrical cause of postpartum death and a frequent cause of mortality in the large population of patients with chronic cardiac or pulmonary disease. Indeed, in hospitalized patients who die, careful autopsy discloses evidence of venous thromboembolism in more than 50 percent of the patients examined. If study is limited to postoperative patients, the incidence at autopsy is even greater. Perhaps most significantly, it has been estimated that a substantial proportion of the deaths due to pulmonary embolism is potentially preventable.



Although the importance of diseases related to or caused by microcirculatory thrombosis and hemorrhage cannot be expressed in statistical terms, its scope can be appreciated by a partial listing of the disciplines or diseases in which such disturbances are involved in an important way. The microcirculation is often a contributory and even primary mechanism for disease in hypertension, stroke, diabetes, infectious and inflammatory disease, autoimmune disease, host-graft rejection, cancer, hemolytic anemias such as sickle cell anemia, drug toxicity, mismatched blood transfusions, liver disease, other diseases of the gastrointestinal tract such as pancreatitis, and of the genitourinary system such as glomerulonephritis. Major advancements in our understanding of the function of the microcirculation may result in health gains in many of these areas.

Thromboembolism induced by contact of the blood with foreign surfaces remains the major unsolved problem in the development of artificial organs or prostheses for extracorporeal circulation of the blood or for implantation within the heart and blood vessels. Thromboembolism is a major obstacle to advances in the medical delivery of care involving artificial heart valves, extracorporeal cardiopulmonary bypass, and cardiac assistance both extracorporeal and intravascular; respiratory assistance through extracorporeal circulation, intravascular catheters, electrodes, and valves for treatment of hydrocephalus; artificial hearts, artificial blood vessels, vascular sutures, and all other applications in which the blood comes in contact with a nonbiologic surface. Artificial devices can only be employed today in applications that involve short periods of contact with the blood, unless their surface area is very small (for example, heart valves), unless



thrombosis is accepted (for example, in velour-lined vascular grafts), unless the surfaces are constantly washed clean in areas of high fluid shear (for example, intra-aortic balloons), or unless their use is supplemented by drugs administered to inhibit hemostatic processes (for example, heparin in cardiopulmonary bypass or hemodialysis). The present utility of artificial organs depends upon compromises demanded by the lack of materials having long-term compatibility with the blood; there are at present no truly nonthrombogenic artificial materials available. Thus, until a nonthrombogenic surface is achieved, no meaningful program for the production of mechanical hearts can be seriously entertained.

Excessive blood loss is one of the major causes of morbidity and death in the United States. It is the leading factor which accounts for mortality associated with trauma and is a critical element in morbidity associated with surgery. The precarious state of iron balance in many women is largely a result of blood lost during the menses. Bleeding into the central nervous system is a major complication of patients with hypertension. Thrombocytopenia, representing a below-normal platelet count, is one of the most common causes of bleeding in clinical medicine. Hemorrhage is a major cause of death in patients with leukemia and other forms of cancer, end-stage kidney disease, cirrhosis of the liver and following excessive irradiation. Excessive blood loss frequently requires replacement of blood and blood products which may themselves be associated with complications such as hepatitis and transfusion reaction.

Although the known hemophilic population of this country is only about 25,000 (a small number compared to the hundreds of thousands of patients with the more common conditions



associated with thrombosis and hemorrhage), hemophilia constitutes a major national health problem for two special reasons. First, the disease requires treatment throughout the lifetime of the patient at a cost that bankrupts the patient and his family both socioeconomically and emotionally, and second, treatment of the disease presents one of the most significant single demands upon the nation's blood resources. The factor VIII content of an estimated three million units of blood (almost one-half of the United States' blood supply in 1970) was used for the care of the hemophilic population in the year 1970-1971. Moreover, expected future use of blood resources will increase because there will be a greater participation of patients in home care programs which require the use of more plasma products, and because, as the life expectancy of the hemophilic patient increases, the number of such patients in the United States utilizing plasma products will grow.

The hemoglobinopathies are genetically determined incurable illnesses which afflict large numbers of American citizens. These diseases are the result of hereditary structural alterations in the hemoglobin molecule which lead to deleterious changes in its molecular properties and function. In this report, the hemoglobinopathies discussed include sickle cell anemia, hemoglobinopathies other than sickle cell, thalassemia, and defects of red cell enzymes and membranes.

Sickle cell disease, which encompasses both sickle cell anemia and its genetic variants, is the most common and serious of the hemoglobinopathies. It affects at birth about one out of 400 American blacks; somewhat less than 50,000 Americans have this disease because some of its victims die in childhood.



Thalassemia apparently results from a deficient (or defective) messenger RNA which controls the synthesis of one of the two types of subunits of hemoglobin. Thalassemia in the homozygous state, which is found in perhaps 5,000 Americans (the prevalence is not known) largely of Mediterranean ancestry, causes severe anemia which generally requires blood transfusions for survival.

Studies of red cell enzymes and red cell membranes are important in the hemoglobinopathies and in blood preservation. Many red cell enzymes have been identified and deficiencies among them are quite uncommon. Two deficiencies, however, are frequently observed: glucose-6-phosphate dehydrogenases deficiency (g.6-PD), a sexlinked trait which occurs in 10 percent of black males and less commonly in males of Mediterranean ancestry; and pyruvate kinase deficiency, an autosomal recessive trait found in both sexes. Other enzyme deficiencies are rare. Still, their effects are of considerable medical interest and significance.



In order to lessen the national impact of blood diseases, a balanced program of basic, interdisciplinary research and clinical application should be designed.

Understanding of the dynamics of hemostasis requires both fundamental research and clinical studies. A century ago, the field of blood coagulation was cultivated in close relationship with the problems of hemostasis. At that time, observations and experiments on thrombosis and coagulation were being performed by investigators who sought answers to practical clinical questions as well as answers to questions of general biologic interest. However, with the advent of specialization this once homogeneous field has become fragmented: cardiologists, surgeons, neurologists, hematologists, pathologists, physiologists, pharmacologists, biochemists, physical scientists, radiologists, geneticists, and epidemiologists have attacked, in relative isolation, the different aspects of the problem which were consonant with their specialized skills.

Despite this fragmentation of skills, substantive advances related to patient care have occurred across lines of specialization in recent years. The anticoagulant heparin was discovered by a medical student while searching for a procoagulant activity in liver. The anticoagulant coumarin drugs were uncovered by chemists during a search for the basis of hemorrhagic spoiled sweet clover disease of cattle. As part of laboratory research into the purification of factor VIII, a chance observation that the antihemophilic globulin was the last plasma protein to go into solution as frozen plasma thawed, led to the development of factor VIII concentrates



that have revolutionized the treatment of hemophilia. Laboratory study of platelet aggregation in vitro has resulted in the recognition of pharmacologic agents that inhibit this process. Some of these drugs are currently undergoing clinical trials as antithrombotic agents. Drawing from these examples, it may be suggested that interdisciplinary research can hasten not only our understanding of thrombogenesis, but can accelerate contributions from diverse fields that will lead to improved prophylaxis, therapy, and diagnosis of the thrombotic process.

Furthermore, both basic research and clinical studies hold potential for the hemoglobinopathies. A major accomplishment in red cell research during the last quarter century has been the delineation of the molecular structure of hemoglobin. However, we are only beginning to understand the molecular interactions which account for the functional properties of the hemoglobin molecule as an oxygen transport protein. Modulation of the oxygen delivery system by other compounds in the red cell has been demonstrated, but much remains to be learned about the complexities of this unique cell. Hence the broad overall problem is the diseases of the red blood cell. Initial goals in basic research are concerned with the delineation, at a molecular level, of the synthesis, assembly, structure and function of the components of the red blood cell, as separate components and as parts of an integrated system.

There are few areas of medicine in which basic research is so intimately correlated with clinical application as in the area of the hemoglobinopathies. The causes, mutations in the genetic material, are known, and in many of the disorders a defect



in a single molecular species has been defined. While more knowledge about the molecular basis of the functions of the red cell is necessary, we are now beginning to visualize approaches to the therapy of these disorders which would dramatically ameliorate their manifestations. Pharmacologic treatment of sickle cell disease may significantly lessen the disability produced by this disorder, and the ability to alter messenger RNA or control the synthesis of hemoglobin subunits would offer far more in the treatment of thalassemia major than any manipulations of our present palliative measures. The emphasis on basic research in red cell disorders is not meant to denigrate the value of good clinical studies designed to define the optimum management of these diseases using therapeutic measures of much greater efficacy than any which are now known will become available. A program of research in the hemoglobinopathies should recognize not only the clinical importance of the diseases, but also the existence of functionally important interactions of many components of the erythrocyte. The red cell, its contents, and its environment constitute an integral system whose behavior is susceptible to definition in molecular terms. From such detailed knowledge of structure and function, new approaches to the management of clinical disorders will be derived. As we begin to perceive these interrelationships in the erythrocyte, it is apparent that research on red cell membranes may ultimately have applications to sickle cell disease, that research on unstable hemoglobins may bear upon the problems of thalassemia, and that research in red cell enzymes will be applicable to the hemoglobinopathies.



PART II

THE PROBLEMS AND PROPOSED PROGRAM



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2.1 THROMBOSIS AND HEMORRHAGE

The mechanisms whereby fluid blood is maintained within the intravascular space are known collectively as hemostasis. The hemostatic mechanisms function both as part of the body's defense against injury and as part of the body's resources to repair that injury. Failure of the complex response to injury may result in hemorrhage; in contrast, distortion of the repair process may lead to thrombosis, wherein a solid mass or plug forms intravascularly from constituents of flowing blood.



The Task Group material is presented in the following sequence:

- The Hemophilias
- Platelets
- Microcirculation
- Vascular Prostheses
- Arterial and Venous Thromboembolism.

The hemophilias are described first because this topic introduces (aside from the problem of hemorrhage secondary to congenital deficiencies in coagulation factors) the role of the clotting procoagulants and inhibitors which are one of the four key aspects of the thrombotic process.

The next section is devoted to the platelets, the second cardinal aspect in intravascular coagulation. The platelet represents a major component of the hemostatic plug. The pathological growth of this plug is the initial morphological evidence of a thrombus, whereas failure of the normal integrity of this plug leads to hemorrhage. This section also demonstrates that the platelet has a wider biological contribution than its function in thrombosis and hemorrhage and leads quite naturally to an examination of the material assembled by the Task Group on Microcirculation.

The microcirculation refers to all small blood vessels and includes, in addition to the blood that circulates through the vessels themselves, the endothelium, subendothelial structures, extravascular supporting and surrounding matrix,



the extravascular fluid environment, the organs and tissues they supply, and, finally, the relatively unexplored area where endothelium and blood constituents are modulated by diverse disease processes. Thus, the microcirculation brings into focus the third important aspect of the thrombotic and hemorrhagic process, namely, the vessel wall.

The subsequent section on vascular prostheses, in addition to demonstrating the critical need for a nonthrombogenic surface, includes the fourth and final key aspect of the thrombotic process, that of the role of fluid dynamics in thrombus formation.

It appears fitting to conclude this section by referring to thrombembolism in the large arteries and veins: first, because their pathogenesis involves the clotting activities, the platelets, the vascular endothelium and blood flow; and, second, because it is in the area of thrombosis in the major vessels that application of the previously described knowledge will lead to the greatest health benefits.

2.1.1 The Hemophilias

The hemophilias represent striking examples of diseases in which basic and clinical research have led to advances in medical knowledge that have revolutionized patient care. Exactly 20 years ago laboratory research provided the first conclusive evidence that what had appeared clinically and genetically until then to be a single disease, hemophilia, stemmed from a deficiency of either one of two trace plasma-clotting proteins with entirely different chemical



properties--factor VIII or factor IX. Surveys of hemophilic patients carried out over the next several years established that about 80 percent of hemophilia resulted from a lack of factor VIII clotting activity (hemophilia A) and about 20 percent of hemophilia resulted from a lack of factor IX clotting activity (hemophilia B).

Investigators in several laboratories developed reliable quantitative assays for factor VIII and factor IX activity in the period from 1955 through 1960. This made possible the quantitative measurement of levels of factor VIII and factor IX activity in the blood of patients, in the blood of known and suspected carriers of the disorders, in bank blood and blood products, and in plasma fractions. Work was greatly facilitated on the separation and purification of these clotting factors from plasma--both for biochemical study and for the preparation of concentrates for clinical use. Moreover, transfused factor VIII activity was shown to have an unusually short intravascular half-disappearance time of only about 10 to 12 hours. These latter data established the unequivocal need for plasma concentrates for repeated infusion to control serious posttraumatic bleeding and surgical bleeding in hemophilic patients.

Fortunately, two types of factor VIII concentrates became available for the treatment of hemophilia A in the early and mid-1960's. Laboratory research methods for the partial purification of small amounts of factor VIII were scaled up by biologic houses into methods permitting the preparation of lyophilized factor VIII concentrates for therapeutic use from large pools of plasma. The development some years earlier of closed plastic-bag systems for blood transfusion



made feasible the application of a simple cryoprecipitate technique for preparing concentrates of factor VIII from single donors, a technique based upon applying an incidental laboratory observation that factor VIII was one of the last plasma proteins to go into solution as frozen plasma thawed. As these two types of concentrates became generally available, the first truly effective management of serious bleeding in hemophilia A became a reality.

The development of an effective factor IX concentrate for use in the U.S. lagged behind, largely because of difficulty in preparing factor IX concentrates free of activated clotting intermediates and of thrombin. Although such concentrates are now available in this country, problems in their preparation, assay, and use remain unsolved.

A new issue in the management of hemophilia A surfaced in the late 1960's. Clinical investigations of patients whose bleeding was uncontrolled by factor VIII replacement therapy established that a small but significant subset of patients developed circulating inhibitors of factor VIII activity. These inhibitors were shown to be antibodies which form as a consequence of prior transfusion of factor VIII. The prevention and management of this complication remains the major purely scientific problem to be solved in the practical management of hemophilia A today.

The above-described scientific advances made mandatory a shift of innovative thrust in clinical research in hemophilia to problems of delivery of care. Limited demonstration programs of the past several years have clearly shown that skilled orthopedic surgery and physiotherapy,



under cover of administration of concentrates, can rehabilitate patients crippled by the sequelae of earlier musculo-skeletal bleeding. Experimental home care programs have been organized in which patients are supplied with concentrate to keep in their homes and are trained to administer concentrate to themselves at the first sign of bleeding. Apparently, this approach greatly improves the quality of life for the hemophilic patient, and vastly reduces morbidity and expense of hospitalization, but it significantly increases the amount of concentrate used per year. How to make and to pay for the increased amounts of concentrate necessary to expand such programs nationally looms as an enormous unsolved problem. For example, study of U.S. blood resources indicates that the current cost of preparation of factor VIII concentrates could exceed \$100 million yearly. If the use of concentrates were to triple, as it conceivably could with the expansion of home care programs nationally and the broadening use of prophylactic therapy, the cost of concentrates for hemophilia A (at present rates) would approximately equal the total yearly operating budget of the National Heart and Lung Institute.

The prevention of hemophilia is a complex and, at times, controversial matter. Except for rare forms, the hemophilias are transmitted by an abnormal recessive gene on the X chromosome (sex-linked recessive inheritance), which means that:

- The disease affects only males.
- All daughters of a hemophilic father are obligatory carriers.



- Each son of a carrier mother has a 50 percent chance of being born with hemophilia.
- Each daughter of a carrier mother has a 50 percent chance of being a carrier; but, being asymptomatic, does not know whether or not she is a carrier.

Through the older techniques of quantitative assay for factor VIII and factor IX clotting activity and the very recently described immunologic techniques to quantitate the amount of antigen in plasma reacting with heterologous antibody to factor VIII, the majority of carriers in the last group above can now be identified.

Nevertheless, a fraction of carriers in that group escape detection by presently available techniques. One may predict, from the Lyon hypothesis of the random inactivation of the X chromosome in the female, that a small residual fraction of carriers will not be identified by any detection method.

A major problem in preventing hemophilia stems from the present failure of genetic counseling. It is unknown to what degree this failure represents lack of use of present genetic counseling facilities or the need for development of greatly improved counseling techniques.

Unless techniques of prevention are improved, the hemophilic population will grow. Reportedly, the median age of the hemophilic population of the U.S. is 11.5 years. If present trends continue, the majority of hemophilic boys will live into adult life, will marry, and will sire children. Moreover, no history of hemophilia in other family members can



be obtained from about one-third of the patients with hemophilia. Apparently, hemophilia stems from a mutation with a high frequency rate that results in a steady input of new patients with hemophilia into the population.

If the diagnosis of hemophilia A and hemophilia B could be made prenatally, then selective abortion could be used to prevent the disease. Fragmentary data indicate that amniotic fluid does not contain antigenic material reacting with a human factor VIII antibody. From present theory of the formation of amniotic fluid, it seems unlikely that amniotic fluid normally contains material derived from factor VIII or factor IX. Consequently, prenatal diagnosis will require the measurement of something in amniotic fluid different from factor VIII or factor IX, but related to factor VIII or factor IX. Genetic studies should be fostered to attempt to link the loci for factor VIII and for factor IX on the X chromosome to the loci for polymorphic traits which could be measured in amniotic fluid.

Abortion of all female fetuses of hemophilic fathers (obligatory carriers) and all male fetuses of known carrier women (50 percent chance of hemophilia) obviously represents a more drastic approach to prevention, but is technically possible today. Amniotic fluid for determination of fetal sex can be obtained at 14 to 17 weeks of gestation. However, the karyotyping procedure needed to determine sex consumes an additional 2 to 3 weeks. Consequently, by the time abortion can be carried out, the hypertonic saline technique must be used, which is not without risk to the mother. If a method could be developed to establish fetal sex at an early enough



gestational age to permit the use of safer techniques of abortion, then this approach to the prevention of hemophilia would undoubtedly come into more widespread use.

The detection of hemophilia is relatively straightforward, but has been difficult in individual cases because of the nature of the required assay techniques. One must establish whether a hemophilic patient has factor VIII deficiency or factor IX deficiency, because the concentrates used to treat factor VIII deficiency do not contain factor IX and vice versa. As already described, quantitative assays exist which permit the accurate diagnosis of factor VIII deficiency and of factor IX deficiency. However, such assays are not available except in select medical centers; therefore, accurate diagnosis is probably delayed in significant numbers of patients. The problem might be solved by establishing training centers throughout the country where pathologists and laboratory technicians from surrounding areas could come for short periods of instruction to carry out these assays. Another solution, not necessarily exclusive of the former, would be to foster the organization of regional referral centers to which patients with suspected bleeding disorders would be sent for definitive diagnosis.

Referral centers could be designed to serve more than one purpose--for example, management of the hemophilic population as well as diagnosis of hemophilia as described above. A very few centers presently exist which provide excellent care for a small segment of the total hemophilic population. Obviously, the possibility of developing many such centers on a national basis, with federal support, for the care of the majority of hemophilic patients deserves



serious consideration. Such centers offer the enormous advantage of concentrating under one roof the necessary personnel to do the following:

- Provide skilled specialists experienced in dealing with all aspects of care of hemophilic patients
- Organize and support home care programs
- Educate the hemophilic patient in all aspects of his disease and provide support to the family of the hemophiliac in making the social and psychological adjustments necessary to cope with the disease
- Participate in clinical research trials of new therapeutic modalities
- Train physicians and paramedical personnel in hemophilia care.

Conceivably, hospitals and clinics in surrounding communities would affiliate with a regional center. With this arrangement, a hemophiliac could attend the center for an initial period of orientation and evaluation and then be referred to a facility close to his home. He would be seen at that facility for less serious medical problems, e.g., for physiotherapy, and would return to the center for infrequent scheduled visits and for major problems such as surgery. The Center would provide periodic meetings and refresher courses for personnel from the affiliated hospitals, which besides transmitting information would serve the added purpose of permitting personnel from the Center and surrounding hospitals to know and trust each other.



The platelet plays a major role in the hemostatic mechanism. Thrombocytes are produced in the megakaryocytes of the bone marrow and ordinarily circulate in the blood as disc-shaped cells which are nonadherent to each other or to normal endothelium. Their unique biological properties reside in the changes which occur when the endothelium is disrupted. Under these circumstances, the platelets form a hemostatic plug. This response of platelets is mainly responsible for the primary arrest of bleeding following injury to a blood vessel. The series of reactions which are involved in the formation of a platelet hemostatic plug have been broadly defined during the past decade. Although many morphologic and biochemical details have been supplied, much more remains to be learned. Platelets adhere to the site of injury by mechanisms which are still relatively poorly understood. Following adhesion, the platelets undergo a "release reaction," with liberation of components which produce accumulation of additional platelets and augment blood coagulation. The mechanism by which the stimulus of adhesion leads to the response of release is unknown, but of utmost importance. Platelets aggregate in response to components released by other platelets, leading to enlargement of the hemostatic plug. A major compound participating in this response is adenosine diphosphate (ADP), but the mechanism by which it causes platelets to bind together has not been identified. Moreover, there is a growing body of data which suggests that ADP is only one of several physiological platelet-aggregating agents, and that there are additional pathways which sensitize the platelet membrane to the action



of ADP. Finally, the platelet hemostatic plug undergoes retraction, yielding increased durability and tensile strength, probably largely in response to thrombin. Platelet contractile protein presumably is involved in this consolidation reaction, but the details of its activation and participation remain to be worked out.

Recent studies indicate that platelets are also involved in the preservation of vascular integrity. This is best illustrated by the increased vascular fragility that occurs in patients with thrombocytopenia. The details of this interaction are completely unknown, and two schools of thought are in competition for the most promising hypothesis. One states that the platelet is incorporated into the endothelial cell; the other postulates a platelet metabolic product which "nourishes" endothelium.

There are numerous practical benefits which would follow from a detailed understanding of the various aspects of platelet function. The first group would pertain to many patients with bleeding disorders. In particular, disorders of platelet function without reduction in number need further clarification. Methods for improving platelet function may have a side application to clinical conditions associated with hemorrhage. Thrombocytopenia is one of the most common causes of bleeding problems in clinical medicine and it is in this area that the platelet-endothelial relationship may be of utmost consequence. Another major aspect of the biological activity of platelets is the implication of platelet aggregation in the development of thrombosis. Since the formation of a platelet aggregate plays an important role in the formation of a thrombus, the most effective prophylactic



therapy in the thrombotic disorders may derive from inhibition of platelet function. Understanding of adhesion, release, aggregation, and retraction may provide suitable target pathways for the development of pharmacologic inhibitors to control or prevent occlusive vascular disease. The dual role of platelets in both hemorrhage and thrombosis, therefore, provides a challenging problem in human physiology with wide implications in clinical medicine.

It is gradually emerging that the platelet has a broader biological contribution than its role in hemostasis as described above. Whereas, under normal circumstances, platelets contribute to endothelial integrity, there are a variety of pathological conditions in which platelets play a detrimental role that may result in vascular injury of various types. These include the following:

- Injured platelets may release factors which increase vascular permeability.
- The response of platelets to immune reactions may result in microcirculatory thrombosis.
- Platelets may play a role in the development of atherosclerosis.
- Platelet aggregates on diseased blood vessels may embolize to the myocardial, cerebral, renal, and peripheral circulation producing a variety of clinical symptoms.
- The release of vasoactive substances from platelets may modify the vascular response in pulmonary embolism and subarachnoid hemorrhage.
- Platelets may be important in certain types of host-defense reactions.



Finally, there are many similarities between the behavior of platelets and of cells found in endocrine, muscle and nerve tissue. Thus, studies of the platelet, an easily accessible cell, may provide important information in other areas of human physiology and clinical medicine. In the latter regard, for example, there is some evidence that platelets may be abnormal in some patients with schizophrenia, multiple sclerosis and Down's syndrome.

Platelets also play an important role in blood transfusion. Platelet transfusion is a major aspect of therapy of patients with thrombocytopenia of diverse etiology and may be important in treating patients with qualitative platelet defects as well. Some of the problems associated with the administration of platelets are dealt with in the Blood Resources Panel Report; only a few of the areas of immediate clinical importance will be noted here.

Improved methods for the efficient collection and preparation of platelet concentrates in a regular blood bank at minimum cost are needed. Improved methods for platelet storage should be sought. Particular attention should be paid to the requirements for room temperature storage, the effects of plastics, problems of sterility and correlation of platelet function tests with hemostatic effectiveness.

A major problem in transfusion therapy is the rapid development of alloimmunity which renders subsequent platelet transfusions ineffective. Better methods for detecting platelet antibodies are needed and the possible use of HL-A typing and other methods for assessing tissue compatibility should be explored. A method for cryopreservation of platelets is



needed. In patients who require long-term platelet support and in whom alloimmunity has developed, cryopreservation may permit the transfusion of platelets from geographically remote HL-A matched sibling donors. Autologous platelets stored by cryopreservation may also be useful in treating patients with malignancies who become thrombocytopenic after chemotherapy or irradiation therapy.

Finally, better guidelines for the clinical use of platelets should be established. This is related to the problem of assessing the danger of bleeding in the thrombocytopenic patient, discussed above. Recent suggestions that small amounts of platelets given continuously may have a greater hemostatic effect than larger amounts given at one time needs further confirmation.

2.1.3 Microcirculation

Many vital life processes are mediated within the microcirculatory environment. These include tissue-oxygenation and energy supply; removal and transport of intermediate metabolic products; maintenance of vessel wall permeability or impermeability; local availability, storage or release of initiators and modulators of both local and circulating homeostatic host defense mechanisms; and regulation of transport of cellular products (e.g., hormones, proteins) for utilization elsewhere. Thrombus formation or other processes resulting in inadequate flow or transport in the microcirculation inevitably result in functional disruption of some or all of these homeostatic processes. The site and extent, as well as the cause for the disrupted flow, govern the type and degree of functional disability manifested by the organism.



Microcirculatory occlusion may occur as a consequence of three pathogenetic mechanisms: there may be a distal involvement of the microcirculation as a consequence of normal vascular occlusion in the corresponding artery or vein; emboli from proximal lesions may lodge in the microcirculation, as in endocarditis; or thrombi may form in situ as a result of local abnormalities. The diagnostic, prophylactic, and therapeutic approach in each case may differ. The following remarks pertain to the latter two mechanisms, since the pathogenesis and consequences of large vessel occlusion are covered under a separate category.

Thromboemboli

Thromboemboli may be the result of fragments detached from localized large vessel thrombi, or they may follow the accumulation of hemostatic material in circulating blood to form masses which embolize because of failure to pass through the microcirculation. In some cases, the mechanism is evident, as in the case of endocarditis, where fragments of vegetations from a damaged or infected heart valve embolize to various organs. Presumably, another example of this mechanism exists in transient ischemic episodes of the central nervous system, with carotid artery thrombi acting as the source. The incidence of morbidity from such processes is unknown.

Present evidence indicates that host mechanisms against thrombus formation in moving blood are extremely effective. However, the concept that platelet aggregates or emboli consisting of fibrin and trapped cells do form in moving, circulating blood is considered to be the main source of



disseminated intravascular coagulation (DIC). Studies concerning failure of these host mechanisms have formed a central theme for previous investigative work. Nevertheless, the notion of intravascularly formed thrombi embolizing to a site remote from localized vascular pathology must still be regarded as hypothetical at present.

Microvasculopathy

The primary hemostatic response involving the platelet-vessel wall reaction in mammals resembles, to a significant extent, the basic cellular defense mechanisms of more primitive animals such as the invertebrates. Human platelets contain intracellular granules similar to the classical lysosomes of polymorphonuclear leukocytes and contribute to the inflammatory response accompanying tissue injury by releasing constituents which may alter blood vessel reactivity. Recent advances in our understanding of hemostasis afford an insight into the potential pathogenesis of microarterial thrombotic disorders, some of which may originate as a result of inflammation. It is useful to consider primary hemostasis as basically an inflammatory response. In this sense, the platelet might be thought of as a special form of leukocyte. Platelets degranulate during the formation of the hemostatic plug and during the interaction with bacteria, viruses and antigen-antibody complexes. Platelets contribute to the inflammatory response accompanying tissue injury by releasing constituents which increase vascular permeability. These constituents reside preformed in circulating platelets.

There is evidence to suggest that platelets do participate in inflammatory responses. These cells accumulate in blood



vessels adjacent to areas of inflammation and tissue damage. Human kidney transplant rejections may be associated with the formation of platelet aggregates in renal vessels. Various stimuli including circulating antigen-antibody complexes, bacteria and endotoxin, as well as endothelial disruption, may lead to platelet aggregation, degranulation and release of lysosomal cationic inflammatory mediators. Other released platelet constituents, such as vasoactive amines, cathepsin A and prostaglandins may also contribute to the propagation of the inflammatory reaction. The possibility has to be considered that platelet aggregates in flowing blood may themselves initiate damage on a normal endothelial surface, leading to vascular lesions in the microcirculation. It is probable that cationic proteins released from aggregated platelets may initiate these early vascular abnormalities.

In the light of these considerations, two potential pathogenetic pathways which might explain the role of platelets in microcirculatory pathology should be considered. An underlying vascular lesion such as a damaged endothelial surface could initiate the formation of a platelet plug. Propagation of emboli might then lead to distal occlusion in the smaller vessels. On the other hand, various intravascular stimuli such as immune complexes and bacteria could result in circulating platelet aggregates, constituents which initiate local vascular injury or distal occlusions. By these two mechanisms, platelets could therefore contribute to a generalized vasculopathy.

Experimental data also suggest that platelets may be important in the interaction between circulating immune complexes and



the microvasculature. Release of factors from platelets which lead to localized increase in vascular permeability results in the deposition of large immune complexes in these localized regions by a process of filtration. The deposited complexes induce inflammatory injury. Thus, under some circumstances, platelets may serve as a focal influence on the pathogenesis of immune vasculitis.

As part of a generalized, systemic vascular disorder, the microcirculation may be widely involved. Established examples of this reaction include the small vessel lesions of diabetes and the lesions seen in rickettsial infections. There is a growing view that certain syndromes manifested as disseminated intravascular coagulation (DIC) may result from primary vasculopathy, in which the microcirculation is an important participant. The hemostatic disorder encountered in thrombotic thrombocytopenic purpura, the hemolytic-uremic syndrome, or Schwartzman-like reactions during the course of sepsis could be examples of such a mechanism.

An additional aspect of microvascular disease concerns the intimal thickening and ultimate narrowing or occlusion of arterioles seen in arteriolosclerosis and hypertension. Recent studies suggest that this type of reaction may occur following endothelial cell detachment. Considerably more information is needed concerning the physiology and turnover of endothelium in man which may serve as one basis for the preservation of blood vessel health and prevention of arteriosclerosis.



The clinical diagnosis and evaluation of microvascular disease has been largely empirical since most assessments, short of tissue diagnosis, are not capable of distinguishing cause from effect. Three main approaches have been used:

- Those that attempt to detect activation of the clotting factors or other blood components
- Those that seek to determine accelerated turnover of clotting factors or platelets
- Those that attempt to identify vascular damage by identifying circulating endothelium in the blood.

Improvements in terms of reliability, specificity, sensitivity and simplicity in all these diagnostic areas are of great importance. Noninvasive techniques are urgently needed which could unequivocally define pathogenetic models.

Disseminated Intravascular Coagulation (DIC)

Disseminated intravascular coagulation (also called defibrination syndrome, consumption coagulopathy and thrombohemorrhagic syndrome) is characterized by the formation of fibrin in the vessels of the microcirculation. Primary target organs are the kidneys, lungs and choroid plexus; but, the adrenals, pancreas, gastrointestinal tract, liver and heart may also be involved.

Clinically, acute disseminated intravascular coagulation is typically accompanied by a mild to severe bleeding tendency. Most frequent are bleeding from puncture sites, easy bruising, ecchymosis and nosebleeds. Gastrointestinal hemorrhage may

be present. Hematuria is a rare symptom. Vaginal bleeding usually accompanies obstetrical complications. Oliguria is fairly common, but anuria is rare. Dyspnea and neurological symptoms may be present.

An acute uncomplicated form of disseminated intravascular coagulation frequently accompanies abruptio placentae. It is characterized by consumption of platelets, fibrinogen, factors V, VIII and XIII, low plasminogen and occasionally borderline low levels of prothrombin and factor X, but normal or high levels of factors VII and IX. This form of DIC has also been described in patients with acute intravascular hemolysis due to acid ingestion and hyposmolarity. A more subacute form may occur in the course of neoplastic diseases or from a retained dead fetus.

In all of these clinical conditions, the blood coagulation mechanism probably is activated by thromboplastic substances. These substances may include circulating decidual tissue, thromboplastin or serum in abruptio placentae; fetal necrotic thromboplastin-like material in the retained dead fetus syndrome; tumor fluid, thromboplastic or necrotic tumor material in patients suffering from neoplastic disease; and a platelet factor III-like activity, or ADP liberated from red cells in patients with acute hemolytic episodes.

A chronic form of disseminated intravascular coagulation is represented by the Kasabach-Merritt syndrome, encountered in patients with giant hemangiomas. Here, activation of coagulation factors probably takes place in the large hemangiomas facilitated by stagnant blood flow. Thus, clearance



mechanisms in the liver and reticuloendothelial system have no opportunity to remove activated coagulation factors from the circulation.

Blockage of these clearance mechanisms by tumor material, erythrocyte membranes and fibrin strands results in diminished efficiency in the removal of activated coagulation factors and further propagates disseminated intravascular coagulation.

The majority of clinical episodes of disseminated intravascular coagulation are self-limited. Typically, the activation of the blood coagulation system leads to the conversion of a small amount of prothrombin to thrombin which is capable of converting substantial amounts of fibrinogen to fibrin monomer. Thrombin itself may enhance the activation of several coagulation factors, thus exerting a feedback effect on intravascular coagulation. On the other hand, thrombin and factor X_a are inactivated rapidly by circulating inhibitors, and factor XI_a is cleared by the liver and the reticuloendothelial system.

Circulating fibrin monomer, if present in large enough amounts, will polymerize to fibrin. However, experimental and clinical evidence has shown that circulating macromolecular complexes containing fibrin monomer or other fibrinogen derivatives may be present in the circulating blood, without evidence of frank consumption coagulopathy. Perhaps of equal importance is the demonstrated "micro-heterogeneity" of normal circulating fibrinogen, certain forms of which are essentially similar to those present in larger amounts in disease states (i.e., fibrin complexes).



Accumulating evidence indicates that the blood clotting and fibrinolytic mechanisms are closely interrelated with other blood enzyme systems which participate in inflammatory and immunological reactions. Two such systems, the kallikrein-kinin vasoactive system and the complement system may be of special importance in human microvascular disease because their activation induces alterations in blood vessel permeability, attracts polymorphonuclear leukocytes and initiates cell membrane damage. Activation of the plasma kallikrein system results in the production of bradykinin which induces vascular permeability, smooth muscle relaxation or contraction (depending upon the tissue), stimulates leukocyte migration and causes pain. These reactions are all characteristic of the inflammatory response to tissue injury, leading many investigators to believe that bradykinin is a primary chemical mediator of inflammation.

The clotting, fibrinolytic and kallikrein systems share activators and inhibitors, and recent evidence suggests that enzymes of one system can initiate activity in the other systems. Hageman Factor (XII), when exposed to a surface such as collagen or a related component of the blood vessel wall, becomes activated and in turn activates the intrinsic coagulation sequence, plasminogen, and the kallikrein system. Plasmin and kallikrein can themselves induce Hageman Factor activation. Plasmin, like kallikrein, is also capable of releasing kinin from plasma. The plasma α_2 -macroglobulin complexes with, and inhibits the proteolytic activity of thrombin, plasmin and kallikrein and is thereby a potential regulator of the interaction of all three enzyme systems.



The complement system, an immune mechanism of defense, consists of eleven distinct proteins which may be activated by immune complexes. The activation of this system results in cell membrane damage, in the elaboration of vasoactive and chemotactic substances, and in the activation of specialized cell functions such as histamine release from mast cells. Plasmin has been shown directly to activate the first component of complement (C1), to interact with the third complement component with the release of a factor chemotactic for neutrophils, and to inactivate the C1 inhibitor, a plasma inhibitor of C1, kallikrein, and coagulation factors XI and XII. In a manner that is incompletely understood, components of complement participate in the initiation of coagulation, platelet aggregation, clot retraction, and in the activation of the fibrinolytic system. The ability of bacterial endotoxin to initiate intravascular coagulation may be in part complement-mediated.

The manner in which these plasma enzyme systems interrelate in microcirculatory thrombosis, vessel wall injury, vasculitis and homograft rejection is not known. Local activation of coagulation factors and of the components of complement may occur in diseases characterized by the presence of circulating immunoglobulin complexes (e.g., systemic lupus erythematosus, glomerulonephritis, and serum sickness). The vascular lesions themselves are characterized by the presence of fibrin, complement and gamma globulin. Depletion of complement, kallikrein and clotting factors has been documented in the blood of patients with certain infectious diseases suggesting not only disseminated intravascular coagulation, but a generalized state of intravascular proteolysis, as well.



Knowledge of the interaction of these circulating enzymatic systems is fragmentary. Future research should explore the nature of these interactions at a molecular level as well as lead to better elucidation of their physiologic function, metabolic interactions, and turnover in the organism. An understanding of how these systems interact may clarify the manner in which the organism reacts to tissue injury and the mechanisms by which the defense reactions may themselves produce disease.

Endotoxemia

Infections caused by gram-negative bacteria are very common. Gram-negative bacteremia has been reported to occur in approximately one percent of hospitalized patients, with fatality rates of 30 to 50 percent. Since there are 30,000,000 acute hospital admissions per year in the United States, there may be 300,000 episodes of gram-negative bacteremia and more than 100,000 fatalities each year from these infections. The lipopolysaccharides of the cell walls of gram-negative bacteria constitute the material known as bacterial endotoxin. Many of the pathophysiologic effects of gram-negative bacteria are undoubtedly due to endotoxin, and this material is probably one of the most important factors causing the morbidity and mortality associated with bacterial infections. Therefore, studies of endotoxins and the mechanisms by which they produce their effects will provide considerable insight into the prevention of the untoward effects of infections.

Prevention of gram-negative sepsis would be an ideal solution for this problem, but since such episodes generally occur in



debilitated patients, or patients in whom there are underlying disorders which predispose them to such infections, this approach is not practical. Endotoxemia is associated with fever, hypotension, and DIC. Endotoxin has been reported to activate the blood coagulation, fibrinolytic, complement and kallikrein systems. Alterations of these systems may have an effect on the microcirculation and cause either thrombosis or hemorrhage depending upon the balance of the various components. In addition, endotoxin may have a direct effect on vascular endothelium. The above-mentioned pathologic alterations can result in irreversible damage by the time they are detected. Therefore, the early and accurate detection of endotoxemia would be a major step forward in the control of the effects of bacterial endotoxemia. Currently, only one method utilizing the horseshoe crab, *Limulus*, is available for the detection of endotoxemia. The assay is practical and has adequate sensitivity for the detection of endotoxemia in most clinical settings, but additional approaches to this diagnosis would be a most valuable asset.

At the present time, the management of patients with endotoxemia is empirical and depends upon the clinical features that are most prominent. For example, shock is treated with vasopressor agents; high fever with agents that reduce temperature; bacterial infection with antibiotics; and evidence of intravascular coagulation with heparin. However, none of these approaches is totally satisfactory, since a high mortality rate for patients with gram-negative sepsis still remains. Recent evidence suggests that treatment of DIC in patients with gram-negative sepsis and shock does not affect the eventual outcome--a result which may reflect irreversible alterations in the microvascular circulation.



Diseases of the Kidney

In experimental nephritis of both the immune complex and antiglomerular basement membrane types, present evidences suggests that one of the mechanisms by which immunological reactions product glomerular injury is the deposition of fibrin or fibrinogen derivatives. Inflammatory lesions of the glomerulus also result from the intravenous injection of thrombin, thromboplastin, or related compounds in various animals. The Shwartzman reaction, resulting from appropriately spaced doses of bacterial endotoxin and other carbohydrates, represents another well-studied example of experimental renal disease in which there is participation of the coagulation and immune systems.

Coagulation within the renal microcirculation has been shown to be a prominent feature of glomerulonephritis, a disease of man of presumed immunological origin. Acute and chronic proliferative glomerulonephritis, the nephritis of lupus erythematosus, anaphylactoid purpura, subacute bacterial endocarditis, as well as the rejection process in renal allografts (see below) are all associated with glomerular and vascular deposition of fibrin. The merit of conducting controlled studies of both a clinical and basic nature relating to pathogenetic mechanisms and their reversal in these diseases is unquestioned.

Host-Graft Rejection (See Blood Resources Panel Report)

The potential for management of diseases characterized by chronic organ failure and replacement with organs from other



human subjects is best exemplified by the striking developments in the area of renal transplantation. One of the main problems relating to renal allografts has been rejection of the grafts by the host. The role of the microcirculatory events in such phenomenon has not been clarified. In human renal allografts, intrarenal fibrin deposition has been noted in acute, hyperacute and chronic rejection. In certain instances, particularly during hyperacute rejection, DIC has also been reported.

The deposition of fibrin is probably secondary to primary immunologic events, such as immune complex attachment to glomeruli or direct endothelial damage. The possible consequences of interrupting the formation of fibrin to reverse the rejection phenomenon have not been carefully assessed, but might be a fruitful area for investigation.

Hyaline Membrane Disease (See Lung Diseases Panel Report)

Hyaline membrane disease (HMD) is the leading cause of death in live-born premature infants. It is an entity related to prematurity and certain maternal complications such as bleeding and diabetes. It is estimated that 25,000 newborns die each year of this disease in the U.S. alone.

The initial predisposing factor in premature infants seems to be immaturity of the lungs with inadequate production of a surfactant material necessary for proper pulmonary expansion. It is particularly the lecithin fraction of the surfactant complex which shows a sudden increase in the last weeks of fetal life due to maturation of the methyltransferase enzyme pathway. It is possible to correlate pulmonary



functional maturity with the ratio of lecithin to sphingomyelin in the amniotic fluid. In preterm infants, the ratio is usually less than 2:1. In such premature infants, atelectasis develops and hypoxia results with all its consequences leading to the full-blown picture of respiratory distress syndrome (i.e., HMD). The pulmonary "hyaline membranes" are most likely the consequence of plasma transudation into the alveoli and subsequent formation of fibrin. The presence of an alveolar fibrin layer is an important pathogenetic mechanism for several reasons. Fibrin forms a barrier-inhibiting adequate gas exchange. In addition, fibrinopeptides, split off from the fibrinogen molecule in the process of clotting, act as vasoconstrictors, thus causing pulmonary vasoconstriction and consequent hypoperfusion. It has also been shown that fibrin inhibits pulmonary surfactant.

The presence of fibrin establishes a self-perpetuating cycle. The initial events leading to HMD are reinforced, and hypoxia and hypercapnia are exacerbated leading to acidosis and finally death in the majority of patients. It is thus logical to suppose that removal of fibrin or prevention of fibrin deposition may result in decrease in mortality. The rationale for clinical trials relating to these suppositions has been as follows. In term infants, plasminogen levels are very low and do not reach normal adult levels until about seven months of age. In premature infants, the levels of plasminogen are even lower. On the other hand, infants seem to have adequate reserves of plasminogen activators of pulmonary origin. These observations have led, therefore, to studies of the effect of administration of plasmin or plasminogen. Preliminary results based upon mortality data suggest that such therapy may be of benefit.



Basic Pathophysiologic Processes

Future progress in these diseases affecting the microcirculation will be dependent upon a more thorough understanding of several basic pathophysiologic processes. The cellular mechanisms governing release of platelet inflammatory mediators and the pharmacological mechanisms by which some of these agents act need to be better clarified. The interaction of the complement system and the platelet surface may significantly influence pathophysiologic processes. Recent evidence suggests that activation of the alternate pathway of complement via the C3 proactivator system may involve platelet surface changes.

The pathogenesis of several human disease states such as thrombotic thrombocytopenic purpura, the hemolytic-uremic syndrome, lupus vasculitis, rheumatoid arthritis, and serum sickness is probably intimately related to inflammatory interactions of platelets and the microvasculature. The pathogenetic role of the platelet plug in thrombotic purpura is reasonably well established, but the etiology of such a disease is still unknown. Antiplatelet therapy designed toward inhibiting platelet aggregation in this disorder may be of immediate clinical benefit. Similar approaches may be applicable to other disorders of the human microvasculature. Secondary microvasculatory platelet plugging, occurring as a result of yet undetermined intravascular stimuli, may play an important role in the pathogenesis of ischemic myocardial and cerebral disease.



2.1.4 Vascular Prostheses

The present ability to employ prosthetic devices in contact with the blood has been achieved, for the most part, through exploitation of natural mechanisms for the control of thrombotic processes. Examples of this are the ability of blood flow to dissipate activated procoagulants and altered platelets, and the natural level of fibrinolysis that restricts the propagation of a fibrin clot; and by inhibition of hemostatic processes through the use of drugs--for example, heparin in cardiopulmonary bypass or extracorporeal hemodialysis. Substantial advances in the use of artificial organs in contact with the blood will require development of nonthrombogenic materials. Although polymers and other materials designed for contact with the blood vary widely in their tendency to induce thrombosis, none can be regarded as truly bland in relation to the blood, and none approach normal endothelium in their blood compatibility.

Significant progress in this field is most likely to result from a basic understanding of the mechanisms of blood-surface interaction. These mechanisms include the detailed analysis of surface structure at the molecular level, the understanding of reactions in the blood induced by contact with various surfaces, the identification of changes in the blood-surface interface that result from contact of various surfaces with blood, and the establishment of criteria for behavior of blood at an interface with prosthetic surfaces that will permit prediction of the subsequent in vivo behavior of artificial materials. Basic research into the mechanisms of thrombus formation in blood and the rheology of blood



will be important components of this effort. Improved understanding of the biochemistry of plasma coagulation and of platelet activity in thrombosis may be exploited in the development of drugs able to suppress thromboembolism in relation to prosthetic devices. Studies of the pathogenesis and pathophysiology of microembolization resulting from blood-prosthetic surface contact will be important to deal with as a major cause of morbidity in the clinical application of artificial organs.

Previous efforts in the field of vascular prosthesis have been hampered by inadequate understanding of the basic mechanisms involved in the interaction of the blood with foreign surfaces, by insufficient attention to the cleanliness and purity of synthetic materials, by insufficient methodology to characterize the surface chemistry of prosthetic materials at the molecular level, and by incomplete understanding of the nature of processes induced within the blood by contact with nonendothelial surfaces. In the past, excessive attention has been paid to applied research and to the development of hardware without thorough understanding of the basic phenomena involved.

In-depth explorations of fundamental questions are essential before attention can be turned constructively to practical applications. Present evidence suggests that a surface can behave as if nonthrombogenic for several reasons:

- The surface may be bland and naturally so unreactive that blood components neither adhere to it nor are conformationally altered by contact with the surface.



- The surface interacts to a limited extent with blood components, either dissolved or cellular, so as to accumulate a stable, nonreactive coating layer.
- The surface is made nonreactive by pretreatment with passivating molecular components before contact with the blood in vivo.
- The surface becomes nonreactive as a result of the development of a coating layer of living cellular elements with the characteristics of endothelium.

At present there are no artificial surfaces available which are completely unreactive with the blood. Even synthetic polymers showing the most extended long-term blood compatibility can be shown to support platlet adherence. The surface chemistry that dictates the reactivity of materials with blood is not well understood. Assessments of gross average surface properties such as wettability and surface charge have proven inadequate to predict the long-term thrombo-resistance of a surface or to permit development of new nonthrombogenic materials according to principles derived from theory. New techniques will be required to describe the surface structure of materials in intimate detail and to characterize the nature and distribution of surface-blood interactions at the molecular level before major advances in this area can be expected. Detailed investigation of the events in the blood occurring as a result of surface contact are essential. New sensitive techniques for the detection of adsorption of blood components upon synthetic surfaces and for changes in the blood induced by surface contact will be required.



There is evidence that surfaces in contact with blood in vivo develop a nonreactive adsorbed coat of blood components and ultimately develop a degree of passivation. The composition and kinetics of formation and alteration of the adsorbed coat require investigation. Elucidation of the circumstances governing the formation of a passive surface film may lead to successful pretreatment of surfaces and development of a bland interfacial layer of biological components. Such simple measures as precoating with solutions of human albumin have been shown to reduce the reactivity of present-day surfaces with the blood. Application of sensitive, analytical techniques to events at the blood-surface interface may lead to important new insights.

Development of surfaces coated with fabric loops or fibers in which thrombotic deposits become tightly enmeshed has resulted in practical clinical application of prosthetic heart valves and vascular grafts. These surfaces become lined with a layer of adherent thrombus that eventually is invaded by living cells to form ultimately a continuous surface coat of endothelium-like tissue. Such a surface appears stable and bland. Large series of patients bearing artificial heart valves and experiencing a low incidence of thromboembolic complications have been reported through the use of this approach. Improved methods for achieving a stable coat of living cells are needed.

In the absence of nonthrombogenic materials, preservation of function of prosthetic devices in contact with the blood depends largely upon considerations of fluid dynamics and the ability of blood flow to dilute and disperse reactive plasma components and altered platelets. There is a need



for additional detailed studies of the rheology of blood in relation to thrombosis. These studies should include analysis of the composition and course of formation of thrombotic deposits, the effect of flow on the interaction of molecular and formed elements in the blood and at the blood-surface interface, and the effect of flow at or near the surface on cell-cell, cell-surface, and plasma-surface interaction.

The ability of drugs affecting platelet function and plasma coagulation to compensate for the thrombotic stimuli of surface contact requires further investigation, particularly with respect to the protection of hemostatic elements from consumption without induction of an unacceptable hemostatic defect. Intimate understanding of the pharmacology of anti-thrombotic agents will require improved insight into the mechanism of hemostasis, the biochemistry of platelet function, and the events leading to fibrin formation.

Since contact of blood with present-day materials leads to initiation of hemostatic processes, including fibrin formation and platelet aggregation, the presence of particulate material in the blood exposed to foreign surfaces is a regular event that causes microembolization and impairment of the function of vital organs. Increased understanding of the pathogenesis of these conditions is required. Improved filters for the removal of microaggregates show promise of controlling many of the deleterious effects of these phenomena.

There is a need for improved techniques to detect the effects of blood-surface interaction on prosthetic surfaces, and for the effects on blood components of such phenomena. Improved



methods for study of the consumption of hemostatic elements, formation of thrombotic deposits on prosthetic surfaces, and alterations in the formed and fluid constituents of blood, including sublethal changes resulting in diminished cell survival, will be valuable contributions. Correlation of in vitro methods for the demonstration of blood-surface interactions with in vivo events will permit quality control of manufactured prosthetic materials, evaluation of materials under development, and detailed studies of mechanisms of surface-induced thrombosis.

Improvements in thrombolytic therapy may permit the restoration of function of prosthetic devices after the development of surface-induced thrombosis and relief of complicating embolization.

2.1.5 Arterial and Venous Thromboembolism

Arterial and venous thrombi begin morphologically as platelet aggregates. In fact, in the artery, thrombosis can be readily visualized as an extension, or as an exaggeration, of the hemostatic plug that forms in response to injury such as may be seen on ulcerative atheromatous plaques of the coronary arteries.

Arterial Thrombosis and Atherosclerosis

Views on the interrelationship between thrombosis and atherosclerosis range from thrombi, fibrin or platelets being the causal initiator of the early atheroma, to the opinion that advanced and stenosing atherosclerotic lesions cause infarction with thrombosis a secondary phenomena. Such thrombi localize proximally to the narrowing atherosclerotic lesion.



Review of all the available evidence strongly suggests that the truth must clearly fall between these two extreme interpretations. The early atheroma, thus, arises independently of the component parts of the thrombus; but thrombotic material (platelet aggregates and fibrin) does later become incorporated into developing atherosclerotic lesions contributing thereby to the latter's growth. Thrombosis superimposed on an ulcerated and advanced atheroma may also be the final event leading to sudden complete occlusion of an artery.

Hemorrhage, deep within a plaque, probably does not produce ischemia. In contrast, ruptured plaques with secondary hemorrhage and with dissection of luminal blood into the plaque provide a nidus for thrombus formation and further ischemia.

Thrombi may also form on unruptured plaques as a result of hemodynamic changes and "hypercoagulability." In some patients dying of myocardial infarction without demonstrable thrombi at autopsy, both platelet and fibrin thrombi may have lysed between death and autopsy.

The gradual evolution of the uncomplicated atheroma, per se, is not a phenomenon that need imbue the physician with a sense of therapeutic urgency. Simple atheromatous lesions occurring in arteries with wide lumens, such as the aorta, rarely enlarge so as to impair effective nutritional blood flow unless secondary thrombosis supervenes. In addition, in peripheral arteries such as the femoral and its branches, the luminal encroachment of an uncomplicated atheroma is frequently compensated for by the richness of the preexisting collateral circulation. In the heart, the myocardium is



protected, in part, by the enormous capacity of a functionally end-arterial system to develop effective compensatory interarterial channels. It is, rather, one of the complications of atherosclerosis--thrombosis--that endows the lesion with much of its clinical significance. If this tendency to thrombosis could be controlled, there is reasonable evidence that atherosclerosis would have a far less serious effect on the normal life span than is presently the case.

Hypercoagulability

It has been almost 300 years since the initial suggestion of systemic hypercoagulability as a cause of thrombosis was made, yet proof of the existence of a hypercoagulable state still remains elusive. Among the various definitions of hypercoagulability, perhaps the one most readily accepted states that hypercoagulability represents a state of circulating blood which requires a smaller amount of a clot initiator to induce intravascular coagulation than is required in a normal subject. This definition has the additional advantage that it can be tested in experimental animal models.

Retarded blood flow has long been associated with thrombogenesis. Although this cumulative association of stasis and thrombosis appears valid, data, both in animals and in man, indicate that retarded blood flow alone does not initiate intravascular coagulation. If this be true, some alternation of the circulating constituents of the blood must be present to trigger intravascular coagulation in areas of retarded blood flow where the intima is normal.



If clotting factors in their activated form do have a role in either the initiation or propagation of thrombi, stasis facilitates the progress of intravascular coagulation by protecting such thrombogenic species from dispersion, from neutralization by circulating inhibitors, and from clearance by the liver. In addition to these three mechanisms, retarded blood flow favors intravascular coagulation by profoundly altering the physical and chemical properties of a column of blood so as to predispose to fibrin formation. The only mechanism in areas of retarded flow operating against thrombosis is the fibrinolytic system.

Clinical Trials

The design of preventive trials is becoming an increasingly important tool for the evaluation of antithrombotic therapy as an increasing number of compounds become available for use in human subjects. The body of ideas and the experience associated with clinical trials point to numerous design characteristics that appear necessary to assure repeatability and interpretability of results, while sufficiency of case material is still an additional problem.

Even where trial designs include randomization, adequate numbers, standardization of procedures, double-blinding and sophisticated statistical analyses, prevention trials are never foolproof and require the exercise of the highest scientific judgment. This skillful use of judgment is not only demanding in its own right, but is heightened by the additional problems, aside from costs and time, attendant upon carrying out an independent repetition of a large-scale human experiment.



Classical Heparin and Coumarin Therapy

A number of arterial and venous thromboembolic phenomena for which the classical anticoagulants (heparin and coumarin compounds) have been recommended as effective prophylactic or therapeutic antithrombotic agents are listed below with indications of the relative benefit derived from anticoagulation.

Acute myocardial infarction*
Old myocardial infarction*
Coronary failure
Angina pectoris

Stroke complete
Stroke in progress
Transient ischemic attacks*
Cerebral embolus**

Acute peripheral arterial occlusion**
Intermittent claudication

Phlebitis**
Pulmonary embolus**
Pulmonary thrombus
Pulmonary hypertension

Hip fracture**
Postpartum
Pelvic surgery
Atrial fibrillation-reversion to normal sinus rhythm

Valve prosthesis**
Disseminated intravascular coagulation**

*Slight benefit from anticoagulation

**Marked benefit from anticoagulation

The above-listed conditions include cardiac, cerebral and peripheral arterial lesions, peripheral venous and pulmonary arterial lesions, and several categories of patients who are at special risk from thromboembolism. Those marked with a double asterisk represent conditions in which the data reflect an unequivocal benefit from anticoagulant therapy, although in some instances modifying clauses are necessary, such as "hip fractures" which refers to individuals over the age of 45 who will remain bedridden for more than a few days.

Those marked with a single asterisk represent conditions in which the gain from anticoagulants is slight: in the case of acute and old myocardial infarction, probably due to the decrease in pulmonary and systemic emboli. Moreover, there is reasonable doubt as to the value of anticoagulants beyond six months following recovery from acute myocardial infarction. In the remaining disease states the value of anticoagulants is either indeterminate or nil.

It is apparent from this formulation that heparin and the coumarin drugs originally were overrated in terms of their antithrombotic capabilities. They are moderately effective on the venous side of the circulation and less so on the arterial side, particularly in organs, such as the heart and brain, that have physiologically end-arterial circulations. Thus, successful therapy, directed toward arterial thromboemboli is achieved largely in the extremities where, because of the rich, preformed interarterial circulation, extensive intravascular coagulation is necessary to produce arterial insufficiency. Therapy with heparin or coumarin compounds is also effective in the microcirculation in



preventing or retarding disseminated intravascular coagulation (DIC) and in decreasing the incidence of emboli originating from thrombi on prosthetic cardiac valves.

From the results of conventional anticoagulant therapy above, distinctions between arterial and venous thrombi present themselves, and it is apparent from a therapeutic view that DIC has more in common with venous than with arterial lesions.

Today the time is ripe to attempt to improve the delivery of prophylactic antithrombotic therapy for arterial thromboembolism for two reasons. First, we have a more sophisticated approach to the proper use of controlled clinical trials. Second, as a result of basic research, we have a variety of new antithrombotic agents for short- and long-term therapy both for primary and secondary prevention. These new agents include antiplatelet aggregants such as aspirin, dipyridamole, prostaglandin E_1 , glycerol guaiacolate, clofibrate and more recently minidose heparin.

Diagnostic Techniques

Invasive techniques using radio-opaque dyes for almost all major arterial circuits (heart, brain, kidney, bowel, extremities) are effective and are continually being improved. What is needed, however, is a reliable noninvasive technique that would localize the obstruction and possibly even differentiate it from an atheroma. Such a technique would help to follow the course of an established arterial thrombotic event including its natural history and its response to therapy. In this regard, isotopic lung and lower leg venous scans are far ahead of their systemic arterial counterparts.



Therapy

The treatment of already formed arterial thrombi or emboli has been largely dependent upon surgical attacks on the obstructed area by a suitable graft. There are several identifiable factors affecting the immediate success of operative therapy, but surgical success rarely guarantees avoidance of postoperative rethrombosis. This phenomenon has suggested the desirability of concomitant fibrinolytic, antithrombotic therapy, or postoperative antithrombotic therapy.

Although thrombolytic therapy has been shown to reduce significantly the size of pulmonary emboli, its value in dissolving coronary and cerebral artery thrombi or thrombi forming at the periphery of infarcts has not yet been conclusively documented. As part of the evaluation of thrombolytic therapy, the following factors must be considered: efficacy of various dosage schedules, local versus systemic routes of administration, comparisons between streptokinase and urokinase, and efforts to reduce the hemorrhagic tendency produced by fibrinolytic agents. Enough data are presently available to attempt a well-designed and well-executed therapeutic trial of thrombolytic therapy in acute myocardial infarction.

The therapeutic use of fractions prepared from snake venoms, which contain many proteolytic enzymes, has been explored largely through the use of an anticoagulant fraction from the Malayan pit viper which has fibrinogenolytic properties. There has been some clinical success and the drug should be subjected to vigorous clinical trial.



The urgency of the physician's concern with acute peripheral venous thrombosis relates to the intimate but unpredictable association between thrombi in peripheral veins and the fatal embolization of these thrombi to the pulmonary arteries. In this context, both venous thrombosis and pulmonary embolism are best viewed as related, common conditions involving intravascular coagulation, in which the clinical diagnosis is often difficult, the prognosis usually good, the tendency to recurrence great, and the mortality, though relatively infrequent, quite unpredictable. If this be true, then many patients will have to be unnecessarily subjected to prophylactic therapy to protect the few from thromboembolic catastrophes, and the risks of therapy must be less than those of the disease.

It is this concern over not recognizing pulmonary emboli, coupled with the need to overtreat--particularly when the therapy itself represents some hazard--that has attracted great interest recently in defining populations at a high enough risk so that all in the group could be subjected to prophylactic therapy regardless of whether a diagnosis of venous thrombosis was or was not made in a particular patient in the group.

Certain risk factors have been identified with varying degrees of reliability: age, immobilization and bedrest prior venous thromboembolism, arterial insufficiency, congestive heart failure, shock, estrogens, gram-negative sepsis, trauma, surgery, parturition, cancer and blood groups.



The therapeutic problem in proving efficacy of a therapy against lethal pulmonary emboli, despite the use of risk factors in selecting the study population, is illustrated by the following example. It can be determined that for every 1,000 patients subjected to a major general surgical procedure, approximately two will die from pulmonary emboli. It can be calculated that if the event rate (the number of fatalities attributable to pulmonary emboli) is 0.002 and if an 80 percent reduction in mortality from therapy is anticipated, then one should require more than 50,000 patients (treated and controls) to show a benefit from an antithrombotic drug against lethal, postoperative pulmonary emboli. If, however, only a 20 percent benefit were expected, in excess of 800,000 patients would be needed in the trial. These comments emphasize (even for a higher attack rate) that clinical trials are of limited value in recognizing small benefits (i.e., such as a 10 or 20 percent gain from a therapeutic procedure) unless the event rate exceeds 25 percent.

2.1.6 Recommendations

A large number of conceivable project areas were identified in the discussion of problems related to thrombosis and hemorrhage in the preceding sections. From the many discussed, the Panel has prepared a summary listing of its major recommendations for implementation of new programs and for extension or expansion of ongoing programs. Because the efforts of six Task Groups were involved in the area of thrombosis and hemorrhage, the listed recommendations represent a synthesis of those which have arisen from the working groups. The recommendations are listed under the four major program

objective categories and are not intended to represent, in any way, a priority rating of projects or programs. The question of priority is addressed in Part III of this report.

Prevention

1. Provide genetic counseling techniques for patients with hemophilia and related disorders.
2. Develop methods of prenatal diagnosis of congenital coagulation disorders.
3. Develop methods of recognizing carriers of hemophilia and related disorders.
4. Educate patients with various congenital disorders of coagulation mechanisms concerning hemorrhage.
5. Educate physicians and paramedical personnel concerning hemorrhage from congenital, drug- or disease-induced platelet defects.
6. Establish centers for clinical investigation of patients with bleeding disorders, and develop prophylactic programs.
7. Identify, refine and possibly eliminate or reduce risk factors for arterial and venous thromboembolism.
8. Educate physicians in the use of prophylactic antithrombotic therapy in disease states where evidence of its value has already been established.
9. Conduct clinical trials of antiplatelet aggregants for prophylaxis of arterial and venous thromboembolism including patients with coronary heart disease and impending stroke.
10. Conduct clinical trials of antithrombotic agents in certain renal diseases such as glomerulonephritis and in host-graft rejection.
11. Conduct clinical trials of fibrinolytic agents in hyaline membrane disease.



Detection and Diagnosis

1. Improve assays for detecting genetic abnormalities in clotting procoagulants, inhibitors and for recognition of carrier states.
2. Improve methods for detecting disorders of platelet function including (a) differentiating between defects in the production or the destruction of platelets; and (b) recognizing enhanced aggregability of platelets.
3. Develop tests that can predict which patients with platelet abnormalities are most likely to bleed.
4. Evaluate usefulness of existing techniques for recognizing disseminated intravascular coagulation (DIC).
5. Develop blood tests that can recognize hypercoagulability or DIC.
 - Sensitive, specific and quantitative immunological and biochemical assays for clotting factors, inhibitors, platelet constituents, thromboplastins, fibrinopeptides A and B, other derivatives of fibrinogen and fibrin; assays of effects of plasmin and plasmin-like enzymes on polypeptides and other blood components; specific assays for recognizing thrombin or thrombin-like action on fibrinogen and other blood components
 - Sensitive and specific assays for endotoxin and for functionally interactive systems such as complement and kallikreins.
6. Develop sensitive assays for detection of subtle forms of tissue or organ damage; namely, products from tissues and organs.
7. Develop effective assays for distinguishing altered rates of turnover of clotting proteins and platelets and for recognizing metabolic intermediates.



8. Establish referral diagnostic centers for identification of various hemorrhagic and thrombotic states--congenital and acquired.
9. Develop noninvasive techniques for recognizing thrombi in coronary and cerebral arteries by isotope scanning
10. Improve techniques for lung scanning and peripheral venous limb scanning.

Treatment and Management

1. Improve materials for factor VIII and IX replacement therapy--human, animal and synthetic including improved concentrates.
2. Develop home care programs for hemophiliacs.
3. Develop techniques to prevent induced inhibitors to clotting factors and management programs for hemophiliacs who have plasma inhibitors.
4. Establish bleeding centers for improved fractionation of clotting factors needed for therapy and for preservation of platelets for platelet transfusions.
5. Conduct clinical trials of thrombolytic therapy in acute myocardial infarction.
6. (See clinical trials of antithrombotic agents, cited under Prevention.)

Rehabilitation

1. Establish regional hemophilia centers for orthopedic, dental, psychiatric and vocational care and guidance.



Biochemistry

1. Isolate, purify and determine physicochemical characterization of each plasma clotting factor and inhibitor including the fibrinolytic enzyme system.
2. Identify role, at molecular level, of each clotting factor and inhibitor in the coagulation process including the fibrinolytic enzyme system.
3. Determine mechanism at molecular level, of active synthesis and catabolism of each clotting factor and inhibitor including the fibrinolytic enzyme system.
4. Define the chemical role of the platelet in the normal hemostatic mechanism.
5. Determine the chemical basis for role of platelets in thrombosis and their interaction with the endothelium.
6. Define mechanisms whereby platelets may be reduced in number or changed in function.
7. Develop methods that correct or improve platelet function in various disorders.
8. Identify the cellular site of synthesis of all clotting factors and inhibitors including the fibrinolytic enzyme system.
9. Define factors regulating platelet production and destruction.
10. Study the relation of lipids to blood coagulation.
11. Determine the activation step of various clotting proteins including fibrinolytic system.
12. Define the biochemical basis for the thrombogenesis of estrogens.
13. Identify the basis of heparin-induced osteoporosis.



14. Establish the relation of endotoxin to coagulation, fibrinolytic and complement systems, and to endothelium and platelets.
15. Establish the relation of viruses to coagulation, fibrinolytic and complement systems, and to endothelium and platelets.
16. Establish the relation of antigen-antibody complexes to coagulation, fibrinolytic and complement systems and to endothelium and platelets.
17. Determine the mechanism of activation of factor XII and the consequent involvement of the coagulation, fibrinolytic, kallikrein and complement systems.
18. Determine factors that produce endothelial damage and that sustain endothelial integrity.

Epidemiology

1. Evaluate further the risk factors in thrombosis including blood groups.
2. Compare incidence and location of thrombosis in different human populations in different countries including comparisons of race and diet.
3. Examine coagulation factors, inhibitors and fibrinolytic systems in different human populations in different countries.
4. Compare thrombosis in coronary arteries and thrombosis in extracranial and intracranial cerebral arteries, as well as in the aorta and the arteries of the lower extremity.

Immunology--Genetics

1. Develop techniques for genetic engineering to overcome genetic defects in coagulation system.
2. Develop tissue transplantation for treatment of hemophilia.



3. Determine the role of the platelet in host defenses.
4. Develop tissue culture production of urokinase.
5. Detect and diagnose thrombosis as a component of an allograft rejection.
6. Determine the effect of immunosuppressive therapy on DIC.

Pathology

1. Establish an organized international plan and registry for assessing the degree of atherosclerosis and thrombosis among patients dying who have known coagulation defects in clotting proteins, inhibitors, or platelets.
2. Determine the role of the platelet in endothelial reaction, in atherosclerosis and in microembolism.
3. Explore platelet ultrastructure through scanning and transmission electron-microscopy and through freeze-etching using new instruments, cytochemistry, immunocytochemistry, and autoradiography to permit more detailed mapping of the chemical organization of the platelet surface, cytoplasm and organelles.
4. Develop automated serial section techniques for study of human arteries.
5. Improve the dating of age of experimental and human thrombi and infarcts.
6. Develop standardized experimental models for producing arterial, venous and microcirculatory thrombosis.
7. Develop animal colonies with specific defects in clotting factors, clot inhibitors, or abnormalities in the fibrinolytic system.
8. Develop primate colonies in which extensive atherosclerotic lesions are produced to study interrelationships of atherosclerosis and thrombosis.
9. Determine the kinds of atherosclerotic lesions apt to develop thrombosis.



Pharmacology

1. Determine the effect of drugs on platelet reactivity.
2. Study vasoactive compounds within the platelet.
3. Develop synthetic and oral fibrinolytic agents.
4. Fractionate snake venoms for antithrombotic activity.
5. Determine chemical structure of heparin.
6. Determine interaction of coumarin compounds with other pharmacological agents.
7. Collect information of unusual responses to antithrombotic therapy (i.e., heparin "emboli").
8. Develop specific and sensitive assays for heparin.
9. Examine the role of heparinoids in antithrombotic therapy.
10. Determine the effect of antithrombotic agents on disseminated intravascular coagulation.

Physiology

1. Improve survival time of transfused replacement therapy for specific defects in coagulation mechanism.
2. Determine the role of platelets in vascular permeability and endothelial integrity.
3. Investigate similarities and differences between platelets and endocrine, muscle and nerve cells.
4. Define the function of the plasma membrane of the platelet.
5. Further elucidate the adhesion, release reaction and aggregation of platelets.



6. Identify the interrelationships between the coagulation system, the fibrinolytic system, the complement system, the kallikrein system, and antigen-antibody reactions.
7. Investigate the clearance of activated clotting species by the reticuloendothelial system.

Surfaces, Blood Flow and Vascular Prostheses

1. Establish an understanding, at the molecular level, of surface structure of materials designed for contact with blood.
2. Identify the effects of blood-surface interaction on the surface and on the blood.
3. Study the passivation of surfaces.
4. Define the needs for various prosthetic materials dependent upon intended application.
5. Elucidate fluid dynamics to minimize thrombus-producing factors.
6. Develop drugs to prevent thromboembolism on prosthetic devices.
7. Examine the mechanism of formation of particulate material in the blood, especially with cardiopulmonary bypass by extracorporeal circulation and storage of blood for transfusion.
8. Determine the pathophysiology of impaired organ function induced by particulate material in the blood.
9. Develop improved apparatus for blood filtration.



2.2 THE HEMOGLOBINOPATHIES (HEREDITARY RED CELL DISORDERS)

The program outlined for the hemoglobinopathies is divided, to some extent arbitrarily, into four sections:

- Sickle Cell Disease and Sickle Cell Trait
- Hemoglobin Variants Other than Hemoglobin S
- Thalassemia
- Red Cell Enzymes and Red Cell Membranes.

2.2.1 Sickle Cell Disease and Sickle Cell Trait

The hemoglobinopathies, of which the most common and serious is sickle cell disease, are genetically determined incurable illnesses which afflict large numbers of American citizens. The heterozygous state, called sickle cell trait, only rarely produces symptoms, and then not of a magnitude of sickle cell anemia. These abnormalities are the result of hereditary structural alterations in the hemoglobin molecule, which lead to deleterious changes in its molecular properties and function.

Sickle cell disease, a term which encompasses sickle cell anemia (the presence of two genes for hemoglobin S) and its genetic variants (a single gene for hemoglobin S plus a gene for another abnormal "interacting" hemoglobin or for thalassemia), affects about one in 400 American blacks at birth. The total number of patients with sickle cell anemia is estimated to be 25,000 to 50,000. Its genetic bases are evident, but the detailed pathogenesis of many of the manifestations is unknown. Patients with sickle cell anemia have



exceedingly variable clinical manifestations. All have a chronic hemolytic anemia which may be mild or severe, and nearly all have episodes of "sickle cell crisis," attacks of pain in joints, chest or abdomen which may last for hours or days. Some patients have severe recurrent crises rendering them unable to complete their education or to work regularly, while a few patients have such crises infrequently, perhaps only once in several years. Occasional patients experience the onset of symptoms in the second decade of life or even later, but, in general, severe symptoms are seen in children with the disease. The longevity of patients with sickle cell anemia is not known. Although many patients survive into the fourth, fifth, or even sixth decade of life, the mortality rate at given ages, particularly in very young children, has not been established. In addition to the chronic anemia and recurrent crises, a host of other secondary manifestations may occur in patients with sickle cell disease, although some patients escape with few of these secondary complications. Orthopedic disabilities, impaired vision (particularly of a few patients with hemoglobin S-C disease), leg ulcers, infections, crises during pregnancy, pulmonary infarctions, renal impairment and gall bladder disease are some of the complications and represent significant disabling manifestations which occur with reasonable frequency.

The clinical manifestations of sickle cell disease are related to the presence of the abnormal hemoglobin which contains a single amino acid substitution in each of one pair (the β pair) of its four subunits. This amino acid substitution leads to polymerization of the deoxygenated hemoglobin which forms "liquid crystals" within the red cell and thus deforms its shape. Sickled red cells lose normal



red cell deformability and consequently cannot traverse the microcirculation. Sickled cells may then occlude small blood vessels with consequent infarction of small areas of organs. The occlusion of vessels and subsequent infarctions resemble thrombotic disease in small vessels in other diseases. Curiously, however, the painful crises, a hallmark of sickle cell anemia usually attributed to vaso-occlusive episodes, have no counterpart in other thrombotic diseases. All of the manifestations of sickling appear to be related to the polymerization of unliganded (deoxygenated) hemoglobin S, whether it comprises the principal hemoglobin of the red cell as in sickle cell anemia, or is associated with an interacting hemoglobin as in hemoglobin S-C disease. No satisfactory treatment of sickle cell disease is now available, although good general supportive care (e.g., prompt treatment of infections, blood transfusions when the anemia is aggravated by infections, and surgical management of certain secondary complication) has an important place in the management of these illnesses, and clinical trials of agents such as cinate are underway. There is little doubt that optimal supportive care can and should be defined, refined and made more generally available, but the best hope for the dramatic amelioration of sickle cell disease lies in an intensified program of basic and clinical research that would yield information of therapeutic value.

2.2.2 Hemoglobin Variants Other than Hemoglobin S

There are now well over 100 different known variants of human hemoglobin and twice as many as are known are probably not detected by present methods. In general, these hemoglobins result from the substitution of a single amino acid in

one of the two pairs of polypeptide chains. Other genetic mechanisms resulting in hemoglobin variants are known, including deletion of an amino acid residue, non-homologous crossing over between linked loci, and chain elongation.

Detailed studies of hemoglobin variants are necessary components of clinical and basic research programs in the hemoglobinopathies. Clinically significant hemoglobin variants are those which, (a) interact with sickle hemoglobin to produce intermediate forms of sickle cell disease, (b) are associated with familial polycythemia or cyanosis, or (c) are associated with accelerated red cell destruction. Each of these classes of abnormal hemoglobin constitutes an important approach to basic research in hemoglobinopathies, and, in addition, hemoglobin variants which are clinically silent constitute important "reagents" for studying hemoglobin function.

Of the hemoglobin variants associated with clinical symptoms, the most important in terms of numbers of individuals affected are those which interact with hemoglobin S. Hemoglobin C, which is found in the heterozygous state in 2 percent of American blacks, interacts with hemoglobin S (Hb S) to yield a clinical syndrome of mild sickle cell disease. A similar clinical syndrome accompanies the presence of Hb S with certain other variants (e.g., Hb D or Hb O) which appear to favor the polymerization of Hb S. Additional variants appear to interact with Hb S only to about the same extent as does hemoglobin A; i.e., the clinical manifestations of the simultaneous presence of the hemoglobin variant and of hemoglobin S are not essentially different from sickle cell trait.



Studies of the interactions of these hemoglobins in the formation of the deoxy polymer of Hb S constitute an important approach to the definition of the binding sites in the polymers. The interactions with Hb S of hemoglobin variants which lack clinical expression should also be studied. The impairment of polymerization is not likely to be clinically evident except in the rare case (Hb Memphis/S), when the variant occurs in a patient with sickle cell anemia. Thus, the hemoglobin variants can provide information about participation of amino acid residues in binding sites in the hemoglobin polymer by virtue of their effect (none, favor, or impair) on polymerization of Hb S.

A second group of clinically significant hemoglobin variants includes those variants in which the clinical manifestations reflect altered oxygen affinity of the variant. Several examples of hemoglobins with high oxygen affinity and familial erythrocytosis have been identified, and the M hemoglobins (in which the pair of hemes is oxidized) and hemoglobins of low O₂ affinity may be accompanied by cyanosis. The recognition of these hemoglobin variants is important in the clinical diagnosis and management of affected patients who have been subjected to complicated and unnecessary diagnostic procedures or who have received inappropriate treatment when the presence of the abnormal hemoglobin was unrecognized. Variants with abnormal oxygen equilibria have been of great importance in basic research on normal hemoglobin structure and function. Correlation of structural and functional properties in these variants has provided important evidence concerning the participation of certain critical amino acid residues in the oxygen transport function of hemoglobin. Continuing identification and studies of such variants can

be expected to increase our knowledge of the structure-function relationships in hemoglobin.

A third group of clinically significant abnormal hemoglobins includes those which are unstable within the red cell. The presence of such unstable hemoglobins is manifested as a chronic familial hemolytic state, with variable anemia and splenomegaly. Heinz bodies (of precipitated hemoglobin) can usually be demonstrated on incubation of the erythrocytes. Unstable hemoglobins with associated hemolytic anemia appear to be rather more common than we had previously suspected and their recognition is important in clinical hematology. The unstable variants provide evidence concerning the structural basis of the stability of normal hemoglobin. Studies of the pathogenesis of the red cell damage induced by the unstable hemoglobin is particularly pertinent to thalassemia, since in the latter, red cell damage is induced by precipitation of hemoglobin subunits. Studies of the synthesis, of the degradation and of the interactions of unstable hemoglobins with red cell membranes may provide data applicable to the pathogenesis of thalassemia.

Primary Structure of Hemoglobin Variants

Detailed examination of hemoglobin variants has in the recent past constituted an important segment of information about human genetics. The studies have included a broad range of information including (a) demonstrations of mechanisms such as unequal crossing over or chain elongation as mutational events, and (b) markers for linkage studies or for tracing the historical origin and migration of populations.



The ascertainment of the primary structure of hemoglobin variants is laborious at this time, but the importance of these variants in both clinical medicine and basic research makes it essential that facilities for studying primary structure, synthesis and function of hemoglobin be supported and expanded. Methodology to simplify the ascertainment of primary structure and new ways of investigating structure-function relationships in hemoglobin should both receive attention in the program of red cell research.

Since many hemoglobin variants will be detected in the newly established screening programs, capabilities for studies of primary structure should be expanded. The facilities of some laboratories now engaged in these studies could be increased and new facilities established. Some informal regionalization for referral of samples should be instituted, and arrangements to achieve full utilization of these unique "reagents" in basic hemoglobin research should be encouraged. Some general remarks about such laboratories are included under Part IV.

2.2.3 Thalassemia

Thalassemia is a hereditary disorder of hemoglobin synthesis. The observed effect of a thalassemia gene is the complete or incomplete suppression of synthesis of a specific subunit (polypeptide chain) of hemoglobin. Several different genetic defects may be included in the term thalassemia: the two most common and important forms of thalassemia result from impaired synthesis of (1) the β polypeptide chains of hemoglobin (β -thalassemia) or (2) the α polypeptide chains of hemoglobin (α -thalassemia).



The homozygous state of β thalassemia, designated Cooley's anemia or thalassemia major, is most commonly found in children of Italian or Greek ancestry. The synthesis of the β chains of hemoglobin is deficient, and such red cells as are produced are damaged by the normal alpha chains. The anemia which results from both defective production and increased destruction of red cells is usually manifest during the first year of life (but not at birth when the β chains have not yet been replaced by the γ chains of fetal hemoglobin). While the clinical manifestations are variable, most children with untreated Cooley's anemia fail to thrive, and are chronically incapacitated by the anemia. The best available treatment is blood transfusion at regular (every two to four weeks) intervals. With amelioration of the anemia by blood transfusions, children with thalassemia major are able to lead more normal lives, but they must still be thought of as children with a severe illness. Transfusion therapy itself confers another set of problems: pyrogenic transfusion reactions, antibody formation to antigens in the transfused red cells and chronic "iron overload" related to the iron of the transfused blood and perhaps to increased absorption of dietary iron. Iron deposited in the skin, liver, heart and pancreas contributes to the later disability of these children. Splenectomy is usually necessary in the second decade to reduce the transfusion requirements. Many patients with thalassemia major have an increased susceptibility to infection, and few survive to the age of 30. Thalassemia major is common in Greece and Italy; the number of patients with this disease in the United States is not known, but the usual estimate is about 5,000.



In the heterozygous state for β thalassemia minor, which is found in each parent of a child with thalassemia major, clinical symptoms are absent, although mild to moderate anemia reflecting a mild impairment of hemoglobin synthesis is generally found. Thalassemia minor (β type) is not uncommon in Americans of Mediterranean ancestry (Greek or Italian), although its exact prevalence is not known. It is also found in American blacks and more rarely in Americans of Northern European ancestry. However, since thalassemia major of the classical transfusion-requiring type is extremely rare in Africans or Afro-Americans, there must be some as yet unexplained difference between the β thalassemia commonly found in black populations and that occurring in persons of Mediterranean ancestry.

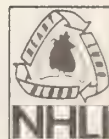
The second common type of thalassemia, α thalassemia, is most commonly encountered in individuals of (1) Oriental ancestry, (2) African ancestry or (3) Mediterranean ancestry. The genetic basis for the different clinical syndromes attributed to α thalassemia are not entirely clear, but the manifestations themselves can be classified into four groups: (1) hydrops fetalis and death of the severely affected fetus, (2) moderately severe anemia with demonstrable excess of β polypeptide chains (Hb H disease), (3) a moderate hypochromic anemia or (4) a "silent" carrier detected only by sophisticated biosynthetic methods. In each of these forms, deficient synthesis of α chains can be demonstrated. Like β thalassemia, α thalassemia in blacks may differ from the Oriental type: hydrops fetalis has been observed only in Orientals, and blacks with hemoglobin H disease generally show smaller amounts of hemoglobin H than do Orientals. There are no firm data on the general effects of α thalassemia on life



expectancy: the most severely affected are dead at birth and the next most severely affected (Hb H disease) would be expected, on clinical grounds, to have some shortening of life span, but individuals with Hb H disease are known to have survived beyond the age of 60.

The diagnosis of β thalassemia major is readily made in early childhood, but specialized facilities (available in many teaching and community hospitals) are necessary for testing the heterozygous state for β thalassemia. In contrast, only the more severe forms of α thalassemia, hydrops fetalis and hemoglobin H disease, are detected with the generally available facilities of good clinical laboratories. We have no proven methods for ready diagnosis of the two milder forms of α thalassemia in large numbers of individuals. (The ascertainment of these milder forms of α thalassemia is based either on studies of the members of the family of patients with the two more severe forms of the disease or on sophisticated laboratory studies which are available only in laboratories engaged in research in thalassemia.)

If both α and β thalassemia are considered together, millions of people in the world are affected by these hereditary disorders. In the United States at this time, it would seem wise to place major emphasis in clinical research on β thalassemia, since the clinically significant forms of α thalassemia are less common and cause much less disability. The most severe form of α thalassemia results in perinatal death rather than disability.



2.2.4 Red Cell Enzymes and Red Cell Membranes

The general objectives concerned with disorders which are based on defects in red cell metabolism (enzymes) or red cell membranes may be conveniently divided into those concerned with: the detection of these disorders, and the effects of other red cell disorders on red cell metabolism and on red cell membranes.

The Detection of Disorders

The detection of disorders of the red cell membranes and red cell metabolism is part of improved diagnosis. Of the red cell enzyme deficiencies, the most commonly encountered is glucose 6 phosphate dehydrogenase (g.6-PD) deficiency, a sex-linked trait which occurs in 10 percent of the black males as well as in lower proportions of Mediterranean or Sephardic Jews. The observed enzymatic deficiency results from a different type of structural alteration in the molecule of the enzyme; the deficiency is generally not clinically manifest, but hemolysis may occur after exposure to certain infections or to drugs (antimalarials or Furoadantin). While mass screening for this deficiency in young men is an appropriate measure in the Armed Forces (because of the deleterious effects of antimalarial agents), such mass screening is not recommended for civilian populations. The emphasis here should rather be placed upon screening as a part of the medical care for an illness.

Red cell membrane defects are evaluated at present in two ways: morphologically with elliptocytosis or spherocytosis evident in the light microscope and further lesions evident



in the electron microscope and by functional defects with demonstration of impaired deformability or ion fluxes. Further morphological studies, particularly of ultrastructure, are needed of both normal and developing red blood cells.

Other methods of measuring constituents of red cell membranes and of measuring function in terms of deformability and rigidity are needed. A more standardized approach to viscosimetry under differing O₂ tensions will be useful for studies of cell flow. In addition, fluxes of nutrients and of other compounds in the red cell may yield further information about membrane function. Red cell metabolic defects include the results of deficiencies of enzymes in the glycolytic pathway, as well as of other enzymatic systems, e.g., methemoglobin reductase. Good screening methods for the detection of g.6-PD deficiency are available, and their use in the hospitalized patient, or in the outpatient who is to receive medication such as Furadantin, should be encouraged.

Better and more readily available methods are needed for testing for pyruvate kinase deficiency, for the types of g.6-PD deficiency which lead to chronic hemolysis and for testing for g.6-PD deficiency in heterozygous females.

The support of a few reference laboratories possessing the capability of diagnosing rarer enzyme deficiencies should be encouraged. Such laboratories are national resources which will facilitate correlations of morphologic changes in red cells and of neurologic deficits in affected patients with specific enzymatic deficiencies. They are a necessary component of research in diagnosis and pathogenesis of these disorders.



The Effects of Other Red Cell Disorders on Red Cell Metabolism and Red Cell Membranes

It is known that the rate of glucose utilization of red cells is considerably lower than the rate at which the individual enzymes of glycolysis are able to metabolize their substrates. Furthermore, in most hereditary disorders affecting the red cell enzymes, the rate of glucose metabolism is normal or may even be increased. Studies are needed to aid our understanding of the factors which control the rate of metabolism of glucose by erythrocytes. The results of such studies may have general application to energy metabolism of other systems. Specifically, it would be necessary to develop accurate methods for the measurement of metabolic intermediates. It will be useful to develop techniques for the purification of red cell enzymes so that their properties can be studied without the presence of disturbing side reactions. The availability of data regarding the functioning of enzymes and the levels of intermediates under various conditions may make possible the construction of computerized models which will predict alterations in the steady state levels of intermediates. Such studies could yield useful information regarding the cause of premature cell death in red cell metabolic disorders.

It has already been shown that the activity of glutathione reductase is affected by riboflavin intake, that GOT levels can be influenced by pyridoxine intake, and that levels of NAD are affected by nicotinic acid intake. Such environmental manipulations of red cell metabolism may prove to be useful in the treatment of disease due to red cell enzyme defects. It is necessary to determine what external agents



affect red cell metabolism and how this information may gainfully be used in treating disorders of red cell metabolism. A particularly pertinent aspect of erythrocyte metabolism is the control of 2, 3-DPG levels. Although some of the environmental factors which affect the level of this important intermediate compound are known, the actual control mechanisms are not. Understanding of these mechanisms might be very important, since their manipulation could permit elevation or decrease of 2, 3-DPG levels for clinical purposes.

For other disorders of red cell metabolism and disorders of red cell enzymes, emphasis should be placed on diagnostic procedures at two levels: (1) development of more reliable, readily available diagnostic procedures which permit classification, if not final diagnosis of the disorder, at the level of teaching and good community hospitals and (2) maintenance and development of a few reference laboratories where detailed studies and diagnoses can be made.

2.2.5 Recommendations

From the discussions of numerous disease problem areas covered in the preceding sections, the Panel has prepared a summary listing of its major recommendations. Recommendations are presented under the four major program objectives. The listing of projects and programs is not intended to convey orders of priority. The question of priority is treated in Part III of this report.



Prevention

1. Sickle Cell

- Increase public awareness and knowledge of sickle cell anemia, its variants and of sickle cell trait to avoid problems with employment, insurance, stigmatization, etc.
- Provide family and marriage counseling.

2. Thalassemia

- Determine frequency of thalassemia in identified target populations of Mediterranean ancestry. This should determine frequency of thalassemia in 2nd and 3rd generation descendants of Mediterranean immigrants and their attitudes about mate selection.
- Determine frequency of thalassemia in blacks from additional study of bloods obtained in current sickle screening programs.
- Develop a plan to register diagnosis of thalassemia major.

3. Red Cell Enzymes and Membranes

- Prevent acquired disorders by removing inciting cause (i.e., artificial heart valves, oxidative drugs and infections).
- Identify drugs that cause hemolysis.

Detection and Diagnosis

1. Sickle Cell

- Establish a screening program--in newborns and later in life.



2. Hemoglobin Variants Other than Hb S

- Develop a simpler diagnostic technique than currently available, particularly use of immunological methods.

3. Thalassemia

- Develop methods of prenatal detection.
- Develop better and less expensive screening tests.

4. Red Cell Enzymes and Membranes

- Emphasize screening the ill patient who might be at risk for complications of enzyme deficiency.
- Improve assays.
- Support special national reference laboratories for diagnosis of very rare enzyme deficiencies.

Treatment and Management

1. Sickle Cell

- Study the natural history of disease which is very variable.
- Determine optimal management of complications.
- Establish a cooperative red cell disease study group patterned after the Leukemia Chemotherapy Group.



2. Thalassemia

- Determine optimal transfusion program for thalassemia major.
- Improve methods for chelation and excretion of iron.
- Collect data on natural history.

3. Red Cell Enzymes and Membranes

- Remove offending drug or control infection for red cell enzyme deficiencies.
- Evaluate possible benefit of splenectomy.

Acquisition of Fundamental Knowledge

1. For sickle cell disease, develop chemotherapeutic agents. Four types are possible:
 - Agents that shift equilibrium between oxy and deoxy forms to favor oxy form.
 - Agents that interfere with polymerization of deoxy hemoglobin S.
 - Agents that interfere with synthesis of or modify the binding of 2, 3-DPG (i.e., cyanate).
 - Agents that interfere with reactions between hemoglobin S and red cell membrane.
2. Understand, at the molecular level, the participation of each amino acid residue in the oxygenation function and the interaction of hemoglobin with intracellular regulatory molecules and with red cell membranes.
3. Determine the structure and formation of Hb S polymers.



4. Develop rational chemotherapy for sickle cell disease.
5. Determine structure and function of Hb variants.
6. Determine function of chemically modified hemoglobins.
7. Explore immunological methods for identification of hemoglobins.
8. Develop specific genetic therapy: isolation of synthesis of hemoglobin genes.
9. Study transcriptional control of chain imbalance.
10. Study translational control of chain imbalance.
11. Elucidate mechanisms of gene switching: fetal to adult Hb.
12. Determine properties of red cell enzymes: electrophoretic behavior, primary sequence, changes with aging, effect on red cell life span, intracellular localization and reactions with Hb and enzymes, alternative pathways in enzyme defects.
13. Determine control mechanisms in red cell glucose metabolism.
14. Manipulate red cell metabolism by environment.
15. Study enzyme structure-function relationships through use of red cell enzymes.
16. Study the structure of red cell membranes.



17. Study red cell membrane function.
18. Establish hemoglobin and thalassemia reference laboratories for study of Hb variants.
19. Establish red cell enzyme reference laboratories.
20. Establish a hemoglobinopathy cooperative study group for three general areas of research:
 - Natural history of sickle cell disease or thalassemia.
 - Best methods of management of secondary complications of these disorders.
 - Therapeutic trials of agents which appear to justify clinical investigation.



PART III

SUMMARY OF PANEL RECOMMENDATIONS



PART III
SUMMARY OF PANEL RECOMMENDATIONS

3.1 INTRODUCTION

This part provides an overall summary of the recommendations of this Panel. The summary consists of two sections, the first dealing with thrombosis and hemorrhage and the second with the hemoglobinopathies.

1. In the first section, five broad types of efforts stand out. The first is the establishment of one or more "demonstration" centers for bleeding disorders relating to the hemostatic mechanism. (There is a set of recommendations concerning similar "demonstration" centers in the section on the hemoglobinopathies.) Within such centers, activity would range widely from counseling patients to training professional personnel to developing improved assays for recognizing specific defects. Proposals relating to such centers could be implemented immediately at modest cost and would result promptly in improved patient care.



2. The second recommendation under thrombosis and hemorrhage deals with the establishment of various comprehensive "registries." Results may be anticipated in 5 to 10 years.
3. The third type of effort recommended under thrombosis and hemorrhage is the development of new technology--for example, the creation of a nonthrombogenic surface and noninvasive diagnostic techniques. These recommendations could be handled on a contract basis with the expectation that useful answers would be achieved in 5 to 10 years.
4. The fourth type of effort recommended under thrombosis and hemorrhage refers to organized multicenter clinical trials for antithrombotic agents and for therapy for sickle cell disease.
5. The final grouping refers to fundamental research recommendations which could probably best be handled by the usual grant mechanism. This area also will bring applicable advances within a period of 2 to 10 years.

These recommendations are listed below in a more specific, outline form. Similar types of effort are listed under the hemoglobinopathies. These recommendations are specifically grouped in that section under demonstration centers, establishment of cooperative red cell disease study group, and therapy research.

3.1.1 Thrombosis and Hemorrhage

1. Demonstration Centers

- Develop techniques for genetic counseling
- Develop techniques for prenatal diagnosis
- Develop techniques for professional and patient education



- Perform clinical investigation of bleeding disorders
- Provide for recognition of carriers of hemorrhage disorders
- Develop improved assays for recognizing genetic abnormalities
- Develop improved methods for detecting disorders of platelet function
- Develop assays to detect DIC and hypercoagulable states
- Provide instruction in home care programs for bleeding disorders
- Train professionals in care of patients with bleeding disorders in fields of orthopedics, dentistry, psychiatric and vocational care.
- Develop improved materials for factors VIII and IX replacement therapy.

2. Registries

- Compare incidence and location of thrombosis and of levels of clotting factors, inhibitors, fibrinolytic enzymes and platelet function in different human populations in different countries
- Establish international registry for assessing degree of atherosclerosis and thrombosis (especially in coronary and cerebral arteries) among autopsied patients who had known abnormalities in clotting proteins, inhibitors, platelets, and fibrinolytic enzymes
- Develop animal colonies with specific abnormalities in clotting proteins, inhibitors, platelets, and fibrinolytic enzymes



- Develop primate colonies in which advanced atherosclerotic lesions are produced to study interrelationships of atherosclerosis and thrombosis (refer to the Heart and Blood Vessel Diseases Panel Report).

3. Techniques

- Develop noninvasive techniques for recognizing thrombi in coronary and cerebral arteries (refer to the Heart and Blood Vessel Diseases Panel Report)
- Develop a nonthrombogenic surface
- Devise improved techniques for fractionation of plasma clotting factors needed for treatment of bleeding diseases (refer to the Blood Resources Panel Report)
- Devise improved techniques for preservation of platelets for therapy (refer to the Blood Resources Panel Report).

4. Clinical Trials

- Evaluate thrombolytic therapy in treatment of acute myocardial infarction
- Evaluate prophylaxis of acute myocardial infarction with antiplatelet aggregants such as aspirin and low-dose heparin
- Evaluate prophylaxis of postoperative pulmonary emboli with antiplatelet aggregants such as aspirin and low-dose heparin
- Evaluate prophylaxis of transient ischemic attack with antiplatelet aggregants
- Evaluate prophylaxis of thrombosis in relation to artificial prostheses with antiplatelet aggregants.

5. Fundamental Research

- Isolate, purify, provide physicochemical characterization and elucidate the intermediary metabolism of each plasma clotting factor and inhibitor including fibrinolytic enzyme system
- Explore platelet ultrastructure through scanning and transmission electron-microscopy and through freeze-etching using new instruments, cytochemistry, immunochemistry and autoradiography to permit more detailed mapping of chemical organization of platelet surface, cytoplasm and organelles
- Establish the relation of (a) endotoxin, (b) viruses, (c) antigen-antibody complexes to platelets, endothelium, coagulation, fibrinolytic, complement and kallakrein systems
- Develop standardized animal models for venous, arterial and microcirculatory thrombosis to evaluate pathogenesis of thrombosis and the influence of drugs, diet, and antithrombotic compounds on plasma clotting factors, inhibitors, fibrinolytic systems, and the initiation of intravascular coagulation.

3.1.2 The Hemoglobinopathies

1. Demonstration Centers

- Develop techniques for family and marriage counseling concerning sickle cell disease, its variants and sickle cell trait
- Develop programs for prenatal detection of thalassemia



- Develop screening programs for newborns and for children with sickle cell disease, its hemoglobin variants and sickle cell trait
- Develop better diagnostic and screening tests for Hb variants other than S and for thalassemia
- Develop techniques for increased public awareness and knowledge of sickle cell anemia, its variants and sickle cell trait
- Establish reference laboratories for diagnosis of rare red blood cell enzyme deficiencies and hemoglobin reference laboratories for structure of Hb variants
- Develop training programs for rehabilitation of physical deformities, psychological and vocational needs of patients with sickle cell disease
- Establish a registry for diagnosis of thalassemia major
- Provide instruction to professionals on screening ill patients who might be at risk from complications of red blood cell enzyme deficiencies
- Improve assays for diagnosis of defects in red blood cell enzymes and membrane.

2. Establishment of Cooperative Red Cell Disease Study Group

(Patterned after the Leukemia Chemotherapy Group)

- Determine natural history of sickle cell disease and thalassemia

- Determine best methods of management of secondary complications of these disorders
- Conduct therapeutic trials of agents which appear to justify clinical investigation such as cyanate.

3. Therapy Research

- For sickle cell disease, develop four types of chemotherapeutic agents:
 - Agents that shift equilibrium between oxy and deoxy forms to favor oxy form
 - Agents that interfere with polymerization of deoxy Hb S
 - Agents that interfere with synthesis of or modify the binding of 2, 3-DPG (i.e., cyanate)
 - Agents that interfere with reactions between Hb S and red cell membrane
- Understand, at the molecular level, the participation of each amino acid residue in the oxygenation function and the interaction of hemoglobin with intracellular regulatory molecules and with red cell membranes
- In relation to therapy research recommended above, answers regarding the following are needed:
 - Structure and formation of Hb S polymers
 - Development of rational chemotherapy for sickle cell disease
 - Structure and function of Hb variants



- Function of chemically modified hemoglobins
- Structure and assembly of red cell membranes
- Functional studies of red cell membranes
- Red cell enzymes: electrophoretic behavior, primary sequence, changes with aging, effect on red cell life span, intracellular localization and reactions with Hb and enzymes, alternative pathways in enzyme defects.



The effort in this section of the report has been to order the Panel recommendations in terms of priorities. Priority ratings are assigned on a five-point scale (i.e., 1 through 5) where "1" indicates the highest priority and "5" the lowest priority. It should be noted that, practically speaking, these priority assignments have limited meaning, with the exception that they do provide a firm indication as to relative priorities among the total set of recommendations provided in this Panel report.

Recommendations are presented in terms of the four primary program objectives: prevention, detection and diagnosis, treatment and management, and rehabilitation. All recommendations assigned at each priority level for each major subject area (i.e., thrombosis and hemorrhage, and the hemoglobinopathies) are presented in Tables 3-1 through 3-7. No recommendations were given a priority number 5 in either major subject area nor was any recommendation given a priority number 4 in the area of hemoglobinopathies.

Table 3-1

THROMBOSIS AND HEMORRHAGE RECOMMENDATIONS ASSIGNED PRIORITY NO. 1

Prevention	Detection & Diagnosis
Establish centers for clinical investigation of patients with bleeding disorders, and develop prophylactic programs. Determine the mechanism of activation of factor XII and the consequent involvement of the coagulation, fibrinolytic, kallikrein and complement systems. Define factors regulating platelet production and destruction. Establish an understanding, at the molecular level, of surface structure of materials designed for contact with blood. Identify the effects of blood-surface interaction on the surface and on the blood. Study passivation of surfaces. Develop drugs to prevent thromboembolism on prosthetic devices. Define the needs for various prosthetic materials dependent upon intended application. Elucidate fluid dynamics to minimize thrombus-producing factors.	Develop effective assays for distinguishing altered rates of turnover of clotting proteins and platelets and for recognizing metabolic intermediates. Establish referral diagnostic centers for identification of various hemorrhagic and thrombotic states—congenital and acquired. Develop blood tests that can recognize hypercoagulability or DIC. (a) Sensitive, specific and quantitative immunological and biochemical assays for clotting factors, inhibitors, platelet constituents, thromboplastins, fibrinopeptides A and B, other derivatives of fibrinogen and fibrin; assays of effects of plasmin and plasmin-like enzymes on polypeptides and other blood components; specific assays for recognizing thrombin or thrombin-like action on fibrinogen and other blood components. (b) Sensitive and specific assays for endotoxin and for functionally interactive systems such as complement and kallikreins. Evaluate usefulness of existing techniques for recognizing disseminated intravascular coagulation (DIC). Develop tests that can predict which patients with platelet abnormalities are most likely to bleed. Isolate, purify, and determine physico-chemical characterization of each plasma clotting factor and inhibitor including the fibrinolytic enzyme system. Identify role, at molecular level, of each clotting factor and inhibitor in the coagulation process including the fibrinolytic enzyme system. →

Table 3-1
(continued)

Treatment & Management	Rehabilitation
Conduct clinical trials of thrombolytic therapy in acute myocardial infarction. Establish bleeding centers for improved fractionation of clotting factors needed for therapy and for preservation of platelets for transfusions. Develop home care programs for hemophiliacs. Define the chemical role of the platelet in the normal hemostatic mechanism. Determine the chemical basis for role of platelets in thrombosis and their interaction with the endothelium. Determine the relation of lipids to blood coagulation. Determine the activation step of various clotting proteins including fibrinolytic system. Establish the relation of endotoxin to coagulation, fibrinolytic and complement systems, and to endothelium and platelets. Determine factors that produce endothelial damage and that sustain endothelial integrity.	Establish regional hemophilia centers for orthopedic, dental, psychiatric and vocational care and guidance.
Detection & Diagnosis (continued) Determine mechanism at molecular level of active synthesis and catabolism of each clotting factor and inhibitor including the fibrinolytic enzyme system. Develop specific and sensitive assays for heparin.	

Table 3-2

THROMBOSIS AND HEMORRHAGE RECOMMENDATIONS ASSIGNED PRIORITY NO. 2

Prevention	Detection & Diagnosis
Provide genetic counseling techniques for patients with hemophilia and related disorders. Develop methods of recognizing carriers of hemophilia and related disorders. Educate patients with various congenital disorders of coagulation mechanisms concerning hemorrhage. Educate physicians and paramedical personnel concerning hemorrhage from congenital, drug- or disease-induced platelet defects. Educate physicians in the use of prophylactic antithrombotic therapy in disease states where evidence of its value has already been established. Conduct clinical trials of antiplatelet aggregants for prophylaxis of arterial and venous thromboembolism including patients with coronary heart disease and impending stroke. Identify, refine and possibly eliminate or reduce risk factors for arterial and venous thromboembolism. Conduct clinical trials of antithrombotic agents in certain renal diseases such as glomerulonephritis and in host-graft rejection. Conduct clinical trials of fibrinolytic agents in hyaline membrane disease. Define the biochemical basis for the thrombogenesis of estrogens. Identify the cellular site of synthesis of all clotting factors and inhibitors including the fibrinolytic enzyme system. Define mechanisms whereby platelets may be reduced in number or changed in function. →	Develop sensitive assays for detection of subtle forms of tissue or organ damage; namely, products from tissues and organs. Improve assays for detecting genetic abnormalities in clotting procoagulants, inhibitors and for recognition or carrier states. Improve methods for detecting disorders of platelet function including (a) differentiating between defects in the production or the destruction of platelets and (b) recognizing enhanced aggregability of platelets. Improve survival time of transfused replacement therapy for specific defects in coagulation mechanism.
	Prevention (continued) Establish the relation of viruses to coagulation, fibrinolytic and complement systems, and to endothelium and platelets. Determine the role of the platelet in host defenses. Determine the role of the platelet in endothelial reaction, in atherosclerosis, and in microembolism. Explore platelet ultrastructure through scanning and transmission electron-microscopy and through freeze-etching using new instruments, cytochemistry, immunochemistry, and autoradiography to permit more detailed mapping of the chemical organization of the platelet surface, cytoplasm and organelles. Study vasoactive compounds within the platelet. →

Table 3-2
(continued)

Treatment & Management	Rehabilitation
Develop techniques to prevent induced inhibitors to clotting factors and management programs for hemophiliacs who have plasma inhibitors. Improve materials for factor VIII and IX replacement therapy—human, animal and synthetic including improved concentrates. Develop methods that correct or improve platelet function in various disorders. Determine the effect of drugs on platelet reactivity. Develop synthetic and oral fibrinolytic agents.	
Prevention (continued) Determine the role of platelets in vascular permeability and endothelial integrity. Further elucidate the adhesion, release reaction and aggregation of platelets. Identify the interrelationships between the coagulation system, the fibrinolytic system, the complement system, the kallikrein system, and antigen-antibody reactions. Examine the mechanism of formation of particulate material in the blood, especially with cardiopulmonary bypass by extracorporeal circulation and storage of blood for transfusion. Establish the relation of antigen-antibody complexes to coagulation, fibrinolytic and complement systems and to endothelism and platelets.	

Table 3-3

THROMBOSIS AND HEMORRHAGE RECOMMENDATIONS ASSIGNED PRIORITY NO. 3

Prevention	Detection & Diagnosis
Develop methods of prenatal diagnosis of congenital coagulation disorders. Compare thrombosis in coronary arteries and thrombosis in extracranial and intracranial cerebral arteries, as well as in the aorta and the arteries of the lower extremity. Develop techniques for genetic engineering to overcome genetic defects in coagulation system. Develop tissue transplantation for treatment of hemophilia. Develop automated serial section techniques for study of human arteries. Improve the dating of age of experimental and human thrombi and infarcts. Develop standardized experimental models for producing arterial, venous and microcirculatory thrombosis. Develop animal colonies with specific defects in clotting factors, clot inhibitors, or abnormalities in the fibrinolytic system. Develop primate colonies in which extensive atherosclerotic lesions are produced to study interrelationships of atherosclerosis and thrombosis. Determine chemical structure of heparin. Determine interaction of coumarin compounds with other pharmacological agents. Investigate similarities and differences between platelets and endocrine, muscle and nerve cells. Define the function of the plasma membrane of the platelet. →	Develop non-invasive techniques for recognizing thrombi in coronary and cerebral arteries by isotope scanning or ultrasound. Improve techniques for lung scanning and peripheral venous limb scanning. Detect and diagnose thrombosis as a component of an allograft rejection.
	Prevention (continued) Determine the pathophysiology of impaired organ function induced by particulate material in the blood. Develop improved apparatus for blood filtration. Determine the kinds of atherosclerotic lesions apt to develop thrombosis.

Table 3-3

(continued)

Treatment & Management	Rehabilitation
Identify the basis of heparin-induced osteoporosis. Develop tissue culture production of urokinase. Examine the role of heparinoids in antithrombotic therapy.	

Table 3-4

THROMBOSIS AND HEMORRHAGE RECOMMENDATIONS ASSIGNED PRIORITY NO. 4

Prevention	Detection & Diagnosis
Examine coagulation factors, inhibitors and fibrinolytic systems in different human populations in different countries. Compare incidence and location of thrombosis in different human populations in different countries including comparisons of race and diet. Evaluate further risk factors in thrombosis including blood groups. Establish an organized international plan and registry for assessing the degree of atherosclerosis and thrombosis among patients dying who have known coagulation defects in clotting proteins, inhibitors, or platelets. Investigate the clearance of activated clotting species by the reticuloendothelial system.	

Table 3-4
(continued)

Treatment & Management	Rehabilitation
Determine the effect of immunosuppressive therapy on DIC. Fractionate snake venoms for antithrombotic activity. Collect information of unusual responses to antithrombotic therapy. (i.e., heparin "emboli"). Determine the effect of antithrombotic agents on disseminated intravascular coagulation.	

Table 3-5

HEMOGLOBINOPATHIES RECOMMENDATIONS ASSIGNED PRIORITY NO. 1

Prevention	Detection & Diagnosis
<u>Sickle Cell</u> Increase public awareness and knowledge of sickle cell anemia, its variants and of sickle cell trait to avoid problems with employment, insurance, stigmatization, etc. <u>Thalassemia</u> Establish a hemoglobinopathy cooperative study group for three general areas of research: - Natural history of sickle cell disease or thalassemia. - Best methods of management of secondary complications of these disorders. - Therapeutic trials of agents which appear to justify clinical investigation. <u>Red Cell Enzymes and Membranes</u> Identify drugs that cause hemolysis. Determine properties of red cell enzymes: electrophoretic behavior, primary sequence, changes with aging, effect on red cell life span, intracellular localization and reactions with Hb and enzymes, alternative pathways in enzyme defects. Determine control mechanisms in red cell glucose metabolism. Manipulate red cell metabolism by environment. Study enzyme structure - function relationships, through use of red cell enzymes. Study the structure of red cell membranes. Study red cell membrane function. →	<u>Sickle Cell</u> Establish a screening program—in newborns and later in life. <u>Hemoglobin Variants other than Hb S</u> Develop a simpler diagnostic technique than currently available, particularly use of immunological methods. Establish hemoglobin and thalassemia reference laboratories for study of Hb variants. <u>Thalassemia</u> Develop better and less expensive screening tests. <u>Red Cell Enzymes and Membranes</u> Support special national reference laboratories for diagnosis of very rare enzyme deficiencies. Establish red cell enzyme reference laboratories.
	Prevention (continued) <u>Related to Hemoglobinopathies in General</u> Understand, at the molecular level, the participation of each amino acid residue in the oxygenation function and the interaction of hemoglobin with intracellular regulatory molecules and with red cell membranes. Determine structure and formation of Hb S polymers. →



Table 3-5
(continued)

Treatment & Management	Rehabilitation
<u>Sickle Cell</u> Establish a cooperative red cell disease study group patterned after the Leukemia Chemotherapy Group. <u>Related to Hemoglobinopathies in General</u> (also applicable to <u>Prevention</u>) For sickle cell disease, develop chemotherapeutic agents. Four types are possible: (a) agents that shift equilibrium between oxy and deoxy forms to favor oxy form, (b) agents that interfere with polymerization of deoxy hemoglobin S, (c) agents that interfere with synthesis of or modify the binding of 2, 3-DPG (i.e., cyanate), (d) agents that interfere with reactions between hemoglobin S and red cell membrane.	<u>Sickle Cell</u> Establish a rehabilitation program for physical disabilities, psychological and vocational needs.
Prevention (continued) Determine structure and function of Hb variants. Determine function of chemically modified hemoglobins. Explore immunological methods for identification of hemoglobins. Develop rational chemotherapy for sickle cell disease.	

Table 3-6

HEMOGLOBINOPATHIES RECOMMENDATIONS ASSIGNED PRIORITY NO. 2

Prevention	Detection & Diagnosis
<u>Sickle Cell</u> Provide family and marriage counseling. <u>Thalassemia</u> Develop a plan to register diagnosis of thalassemia major.	<u>Red Cell Enzymes and Membranes</u> Emphasize screening the ill patient who might be at risk for complications of enzyme deficiency. Improve assays. <u>Thalassemia</u> Develop methods of prenatal detection.

Table 3-6
(continued)

Treatment & Management	Rehabilitation
<u>Sickle Cell</u> Study the natural history of disease which is very variable. Determine optimal management of complications. <u>Thalassemia</u> Determine optimal transfusion program for thalassemia major. Collect data on natural history. Improve methods for chelation and excretion of iron.	

Table 3-7

HEMOGLOBINOPATHIES RECOMMENDATIONS ASSIGNED PRIORITY NO. 3

Prevention	Detection & Diagnosis
<u>Thalassemia</u> Determine frequency of thalassemia in identified target populations of Mediterranean ancestry. This should include determination of frequency of thalassemia in 2nd and 3rd generation descendants of Mediterranean immigrants and their attitudes about mate selection. Determine frequency of thalassemia in blacks from additional study of bloods obtained in current sickle screening programs. <u>Red Cell Enzymes and Membranes</u> Prevent acquired disorders by removing inciting cause (i.e., artificial heart valves, oxidative drugs and infections).	

Table 3-7
(continued)

Treatment & Management	Rehabilitation
<u>Red Cell Enzymes and Membranes</u>	
Remove offending drug or control infection for red cell enzyme deficiencies.	
Evaluate possible benefit of splenectomy.	
<u>Thalassemia</u>	
Develop specific genetic therapy: isolation of synthesis of hemoglobin genes.	
Study transcriptional control of chain imbalance.	
Study translational control of chain imbalance.	
Elucidate mechanisms of gene switching: fetal to adult Hb.	

PART IV

THE LEGISLATION AND THE PROPOSED PROGRAM



PART IV
THE LEGISLATION AND THE PROPOSED PROGRAM

Ten specific program requirements are delineated by the National Heart, Blood Vessel, Lung, and Blood Act of 1972. This section correlates the major recommendations developed by the Task Groups of the Blood Diseases Panel with the 10 legislative requirements. Each of the 10 legislative points is reproduced verbatim from the 1972 Act and is followed by a listing of recommended project areas which relate to it; the 10 points are listed sequentially in Appendix B. Recommended project areas are grouped under each of the two major Problem Areas considered by the Blood Diseases Panel: Thrombosis and Hemorrhage and Hemoglobinopathies.

Tables and figures are included in Appendix B which summarizes the more detailed project areas defined by the seven Task Groups of the Blood Diseases Panel. These include figures which graphically depict Task Group of



the legislative categories and major objective categories, as well as composite figure for all Task Groups. Appendix C lists the problems, approaches, and project areas developed by each Task Group.



"... investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases; ..."

4.1.1 Thrombosis and Hemorrhage

1. Identify, refine and possibly eliminate or reduce risk factors for arterial and venous thromboembolism.
2. Compare incidence and location of thrombosis in different human populations in different countries including comparison of race and diet.
3. Examine coagulation factors, inhibitors and fibrinolytic systems in different human populations in different countries.
4. Compare thrombosis in coronary arteries and thrombosis in extracranial and intracranial cerebral arteries, as well as in the aorta and the arteries of the lower extremities.
5. Study methodology of clinical trials.

All of the above are also included under Legislative Requirement No. 2--basic biological processes and mechanisms/epidemiology.

6. Establish an organized, international plan and registry for assessing the degree of atherosclerosis and thrombosis among patients dying who have known coagulation defects in clotting proteins, inhibitors or platelets. (See Legislative Requirement No. 2--basic biological processes and mechanisms/pathology.)



4.1.2 The Hemoglobinopathies

1. For thalassemia, determine frequency of disease in identified target populations of Mediterranean ancestry and determine frequency of thalassemia in 2nd and 3rd generation descendants of Mediterranean immigrants and their attitudes about mate selection.
2. Determine frequency of thalassemia in blacks from additional study of bloods obtained in current sickle screening program.
3. Develop a plan to register diagnosis of thalassemia major.
4. Red cell enzymes--prevent acquired disorders by removing inciting causes (i.e., artificial heart valves, oxidative drugs and infections).
5. Study the natural history of sickle cell disease which is very variable.
6. For thalassemia, collect data on natural history.



"... studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena; ..."

4.2.1 Thrombosis and Hemorrhage

Biochemistry

1. Isolate, purify and determine physicochemical characterization of each plasma clotting factor and inhibitor including the fibrinolytic enzyme system.
2. Identify role, at molecular level, of each clotting factor and inhibitor in the coagulation process including the fibrinolytic enzyme system.
3. Determine mechanism, at molecular level, of active synthesis and catabolism of each clotting factor and inhibitor including the fibrinolytic enzyme system.
4. Define the chemical role of the platelet in the normal hemostatic mechanism.
5. Determine the chemical basis for role of platelets in thrombosis and their interaction with the endothelium.
6. Define mechanisms whereby platelets may be reduced in number or changed in function.
7. Develop methods that correct or improve platelet function in various disorders.
8. Identify the cellular site of sythesis of all clotting factors and inhibitors including the fibrinolytic enzyme system.
9. Define factors regulating platelet production and destruction.
10. Study the relation of lipids to blood coagulation.



11. Determine the activation step of various clotting proteins including fibrinolytic system.
12. Define the biochemical basis for the thrombogenesis of estrogens.
13. Identify basis of heparin-induced osteoporosis.
14. Establish the relation of endotoxin to coagulation, fibrinolytic and complement systems, and to endothelium and platelets.
15. Establish the relation of viruses to coagulation, fibrinolytic and complement systems and to endothelium and platelets.
16. Establish the relation of antigen-antibody complexes to coagulation, fibrinolytic and complement systems and to endothelium and platelets.
17. Determine the mechanism of activation of factor XII and the consequent involvement of the coagulation, fibrinolytic, kallikrein and complement systems.
18. Determine factors that produce endothelial damage and that sustain endothelial integrity.

Epidemiology

1. Evaluate further the risk factors in thrombosis including blood groups.
2. Compare incidence and location of thrombosis in different human populations in different countries including comparisons of race and diet.
3. Examine coagulation factors, inhibitors and fibrinolytic systems in different human populations in different countries.
4. Compare thrombosis in coronary arteries and thrombosis in extracranial and intracranial cerebral arteries, as well as in the aorta and the arteries of the lower extremities.
5. Study of methodology of clinical trials.



Immunology--Genetics

1. Develop techniques for genetic engineering to overcome genetic defects in coagulation system.
2. Develop tissue transplantation for treatment of hemophilia.
3. Determine the role of the platelet in host defenses.
4. Develop tissue culture production of urokinase.
5. Detect and diagnose thrombosis as a component of an allograft rejection.
6. Determine the effect of immunosuppressive therapy on DIC.

Pathology

1. Establish an organized international plan and registry for assessing the degree of atherosclerosis and thrombosis among patients dying who have known coagulation defects in clotting proteins, inhibitors or platelets.
2. Determine the role of the platelet in endothelial reaction, in atherosclerosis and in microembolism.
3. Explore platelet ultrastructure explored through scanning and transmission electron-microscopy and through freeze-etching using new instruments, cytochemistry, immunochemistry and autoradiography to permit more detailed mapping of the chemical organization of the platelet surface, cytoplasm and organelles.
4. Develop automated serial section techniques for study of human arteries.
5. Improve the dating of age of experimental and human thrombi and infarcts.
6. Develop standardized experimental models for producing arterial, venous and microcirculatory thrombosis.



7. Develop animal colonies with specific defects in clotting factors, clot inhibitors or abnormalities in the fibrinolytic system.
8. Develop primate colonies in which extensive atherosclerotic lesions are produced to study interrelationships of atherosclerosis and thrombosis.
9. Determine the kinds of atherosclerotic lesions apt to develop thrombosis.

Pharmacology

1. Determine the effect of drugs on platelet reactivity.
2. Study vasoactive compounds within the platelet.
3. Develop synthetic and oral fibrinolytic agents.
4. Fractionate snake venoms for antithrombotic activity.
5. Determine chemical structure of heparin.
6. Determine interaction of coumarin compounds with other pharmacological agents.
7. Collect information of unusual responses to antithrombotic therapy (i.e., heparin "emboli").
8. Develop specific and sensitive assays for heparin.
9. Examine the role of heparinoids in antithrombotic therapy.
10. Determine effect of antithrombotic agents on disseminated intravascular coagulation.

Physiology

1. Improve survival time of transfused replacement therapy for specific defects in coagulation mechanism.
2. Determine the role of platelets in vascular permeability and endothelial integrity.



3. Investigate similarities and differences between platelets and endocrine, muscle and nerve cells.
4. Define the function of the plasma membrane of the platelet.
5. Further elucidate the adhesion, release reaction and aggregation of platelets.
6. Identify the interrelationships between the coagulation system, the fibrinolytic system, the complement system, the kallikrein system, and antigen-antibody reactions.
7. Investigate the clearance of activated clotting species by the reticuloendothelial system.

Surfaces, Blood Flow and Vascular Prosthesis

1. Establish an understanding, at the molecular level, of surface structure of materials designed for contact with blood.
2. Identify the effects of blood-surface interaction on the surface and on the blood.
3. Study the passivation of surfaces.
4. Define the needs for various prosthetic materials dependent upon intended application.
5. Elucidate fluid dynamics to minimize thrombus-producing factors.
6. Develop drugs to prevent thromboembolism on prosthetic devices.
7. Examine the mechanism of formation of particulate material in the blood, especially with cardiopulmonary bypass by extracorporeal circulation and storage of blood for transfusion.
8. Determine the pathophysiology of impaired organ function induced by particulate material in the blood.



9. Develop improved apparatus for blood filtration.

4.2.2 The Hemoglobinopathies

1. For sickle cell disease, develop chemotherapeutic agents. Four types are possible:

- Agents that shift equilibrium between oxy and deoxy forms to favor oxy form
- Agents that interfere with polymerization of deoxy hemoglobin S
- Agents that interfere with sythesis of or modify the binding of 2, 3-DPG (i.e., cyanate)
- Agents that interfere with reactions between hemoglobin S and red cell membrane.

2. Understand, at the molecular level, the participation of each amino acid residue in the oxygenation function and the interaction of hemoglobin with intracellular regulatory molecules and with red cell membranes.

3. In relation to (2) above:

- Determine the structure and formation of Hb S ploymers
- Develop rational chemotherapy for sickle cell disease
- Determine structure and function of Hb variants
- Determine function of chemically modified hemoglobins
- Study the structure of red cell membranes
- Determine properties of red cell enzymes: electrophoretic behavior, primary sequence, changes with aging, effect on red cell life span, intracellular localization and reactions with Hb and enzymes, alternative pathways in enzyme defects.



4. Determine control mechanisms in red cell glucose metabolism.
5. Manipulate red cell metabolism by environment.
6. Study electrophoresis of red cell enzymes.
7. Study enzyme structure-function relationships through use of red cell enzymes.
8. Establish hemoglobin and thalassemia reference laboratories for study of Hb variants.
9. Establish red cell enzyme reference laboratories.
10. Conduct immunological studies of Hb.
11. Establish a hemoglobinopathy cooperative study group for three general areas of research:
 - Natural history of sickle cell disease or thalassemia
 - Best methods of management of secondary complications of these disorders
 - Therapeutic trials of agents which appear to justify clinical investigation.



"... research into the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases; ..."

4.3.1 Thrombosis and Hemorrhage

1. Develop methods of prenatal diagnosis of congenital coagulation disorders.
2. Develop methods of recognizing carriers of hemophilia and related disorders.
3. Improve assays for detecting genetic abnormalities in clotting procoagulants, inhibitors and for recognition of carrier states.
4. Improve methods for detecting disorders of platelet function including (a) differentiating between defects in the production or the destruction of platelets; and (b) recognizing enhanced aggregability of platelets.
5. Develop tests that can predict which patients with platelet abnormalities are most likely to bleed.
6. Develop blood tests that can recognize hypercoagulability of DIC.
7. Develop sensitive assays for detection of subtle forms of tissue or organ damage; namely, products from tissues and organs.
8. Develop effective assays for distinguishing altered rates of turnover of clotting proteins and platelets and for recognizing metabolic intermediates.
9. Improve materials for factors VIII and IX replacement therapy--human, animal, and synthetic, including concentrates.



10. Develop techniques to prevent induced inhibitors to clotting factors and management programs for hemophiliacs who have inhibitors.

4.3.2 The Hemoglobinopathies

1. For sickle cell, establish a screening program--in newborns and later in life.
2. For hemoglobin variants other than hemoglobin S, develop a simpler diagnostic technique than currently available, particularly use of immunological methods.
3. For thalassemia, develop methods of prenatal detection.
4. For thalassemia, develop better and less expensive screening tests.
5. For disease of red cell enzymes and membranes, emphasize screening the ill patient who might be at risk for complications of enzyme deficiency.
6. For the disease of red cell enzymes and membranes, develop improved assays.
7. Support special national reference laboratories for diagnosis of very rare enzyme deficiencies.
8. For thalassemia, determine optimal transfusion program for thalassemia major.
9. For thalassemia, improve methods for chelation and excretion of iron.
10. For red cell enzyme diseases, evaluate possible benefit of splenectomy.



"... establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases; ..."

4.4.1 Thrombosis and Hemorrhage

1. Develop noninvasive techniques for recognizing thrombi in coronary and cerebral arteries by isotope scanning and ultrasound.
2. Improve techniques for lung scanning and peripheral venous limb scanning.
3. (See subsection under section 4.2.1 - Surfaces, Blood Flow and Vascular Prosthesis).

4.4.2 The Hemoglobinopathies

None



"... establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases; ..."

4.5.1 Thrombosis and Hemorrhage

1. Provide genetic counseling techniques for patients with hemophilia and related disorders.
2. Establish centers for clinical investigation of patients with bleeding disorders, and develop prophylactic programs.
3. Conduct clinical trials of antiplatelet aggregants for prophylaxis of arterial and venous thromboembolism including patients with coronary heart disease and impending stroke.
4. Conduct clinical trials of antithrombotic agents in certain types of renal diseases such as glomerulonephritis and in host-graft rejection.
5. Conduct clinical trials of fibrinolytic agents in hyaline membrane disease.
6. Evaluate usefulness of existing techniques for recognizing disseminated intravascular coagulation (DIC).
7. Establish referral diagnostic centers for identification of various hemorrhagic and thrombotic states--congenital and acquired.
8. Develop home care programs for hemophiliacs.
9. Conduct clinical trials of thrombolytic therapy in acute myocardial infarction.



4.5.2 The Hemoglobinopathies

1. Provide family and marriage counseling for patients with sickle cell disease.
2. Conduct trials to determine optimal management of complications of sickle cell disease.
3. Establish a cooperative red cell disease study group.
4. Establish a rehabilitation program for physical disabilities, psychological and vocational needs for patients with sickle cell disease.



"... studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, factionalization, and distribution of it and its products; ..."

4.6.1 Thrombosis and Hemorrhage

Develop bleeding centers for improved fractionation of clotting factors needed for therapy and for preservation of platelets for platelet transfusions.

4.6.2 The Hemoglobinopathies

Devise methods for obtaining blood needed for transfusions for patients with hemoglobinopathies.

"... education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases."

4.7.1 Thrombosis and Hemorrhage

1. Educate physicians and paramedical personnel concerning hemorrhage from congenital, drug- or disease-induced platelet defects.
2. Educate physicians in the use of prophylactic anti-thrombotic therapy in disease states where evidence of its value has already been established.

4.7.2 The Hemoglobinopathies

In regard to red cell enzymes deficiencies, inform physicians of offending drugs and the need to control infections.

"... public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources; ..."

4.8.1 Thrombosis and Hemorrhage

Educate patients with various congenital disorders of coagulation mechanisms concerning hemorrhage.

4.8.2 The Hemoglobinopathies

Increase public awareness and knowledge of sickle cell anemia, its variants and of sickle cell trait to avoid problems with employment, insurance, stigmatization, etc.



"... establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases; ..."

4.9.1 Thrombosis and Hemorrhage

1. Conduct clinical trials of antithrombotic agents in certain renal diseases in children (also under section 4.5.1).
2. Conduct clinical trials of fibrinolytic agents in hyaline membrane disease (also under section 4.5.1).
3. Educate children with various congenital disorders of coagulation mechanisms concerning hemorrhage (also under section 4.8.1).
4. Establish centers for clinical investigation of children with bleeding disorders and develop prophylactic programs (also under section 4.5.1).
5. Develop home care programs for children with hemophilia (also under section 4.5.1).

4.9.2 The Hemoglobinopathies*

1. For sickle cell, establish a screening program--in newborns as well as in older age groups.
2. For hemoglobin variants other than Hb S, develop a simpler diagnostic technique than currently available, particularly use of immunological methods.

*All of Research under 4.4 applies to 4.9 as well.



3. For thalassemia, develop methods of prenatal detection.
4. For thalassemia, develop better and less expensive screening tests.
5. For disease of red cell enzymes and membranes, emphasize screening the ill patient who might be at risk for complications of enzyme deficiency.
6. For disease of red cell enzymes and membranes, develop improved assays.
7. Support special national reference laboratories for diagnosis of very rare enzyme deficiencies.
8. Establish a rehabilitation program for physical disabilities, psychological and vocational needs of patients.



"... establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services."

4.10.1 Thrombosis and Hemorrhage

None

4.10.2 The Hemoglobinopathies

None



APPENDIX A

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APPENDIX B

PROJECT AREA DISTRIBUTION ANALYSIS



APPENDIX B
PROJECT AREA DISTRIBUTION ANALYSIS

This appendix presents two categories of data displays resulting from analysis of project areas identified by each task group:

- The percentage distribution of project areas with respect to the 10 legislative requirements and
- The percentage distribution of project areas with respect to the four program objectives.

These results were obtained by a subjective comparison of each project area against the legislation requirements and objectives. These distributions do not reflect the relative manpower or funding required in any objective or legislative category since they are based only on the number of project areas identified.



1. Distribution of Project Areas with Respect to the Legislation

Table B-1 presents, on a task group basis, the percentage of project areas which relate to specific legislative planning requirements. The percentage distribution for all the task groups as a composite is shown in Figure B-1 and Figure B-2 presents the percentage distribution for each task group. The 10 legislative requirements are as follows:

"... (1) investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;

"(2) studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena;

"(3) research into the development, trial, and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases;

"(4) establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases;



"(5) establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for, such diseases;

"(6) studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products;

"(7) the education and training of scientists, clinicians, and educators, in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases;

"(8) public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources;

"(9) establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic diseases) and for the development and demonstrations of diagnostic, treatment, and preventive approaches to these diseases; and

"(10) establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services..."



Table B-1
DISTRIBUTION OF PROJECT AREAS WITH RESPECT TO
THE LEGISLATIVE REQUIREMENTS

Task Group	No. of Project Areas	Legislative Requirement									
		1	2	3	4	5	6	7	8	9	10
Hemophilia and Other Bleeding Disorders	82	2%	63%	28%	4%	11%	0	1%	6%	4%	0
Disorders of Hemostasis Due To Platelet Abnormalities	55	7%	69%	47%	4%	2%	2%	5%	0	0	0
Microcirculatory Thrombosis	33	27%	67%	42%	12%	12%	0	0	0	4%	0
Thromboembolism in Relation to Prosthetic Devices	43	0	49%	74%	26%	0	0	0	0	0	0
Venous Thrombosis and Pulmonary Embolism	55	38%	24%	51%	16%	22%	0	7%	7%	2%	0
Arterial Thromboembolism	38	39%	32%	34%	8%	0	0	0	0	0	0
Hemoglobinopathies	85	11%	46%	29%	4%	18%	1%	2%	6%	0	0
TOTAL	391	13%	51%	41%	9%	10%	1%	3%	4%	2%	0

Figure B-1
COMPOSITE FOR ALL TASK GROUPS

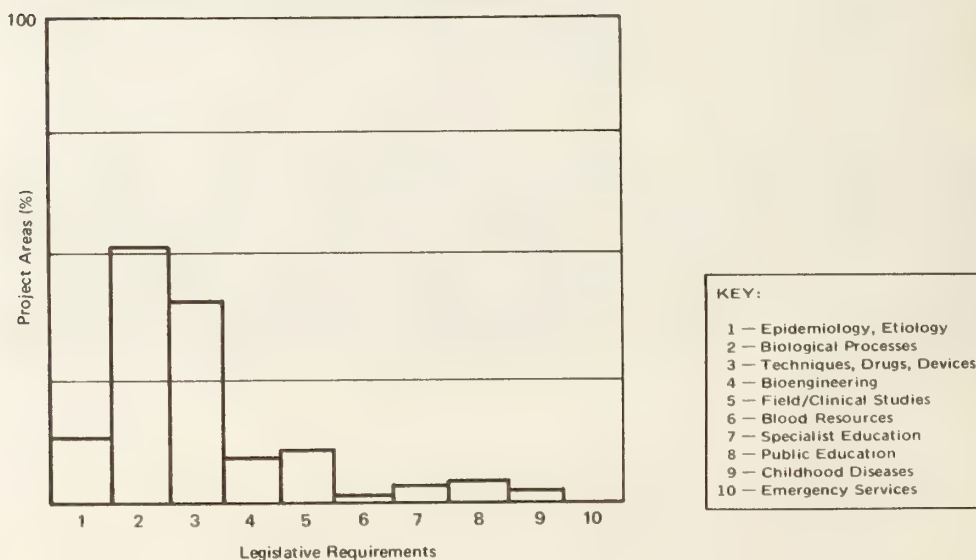
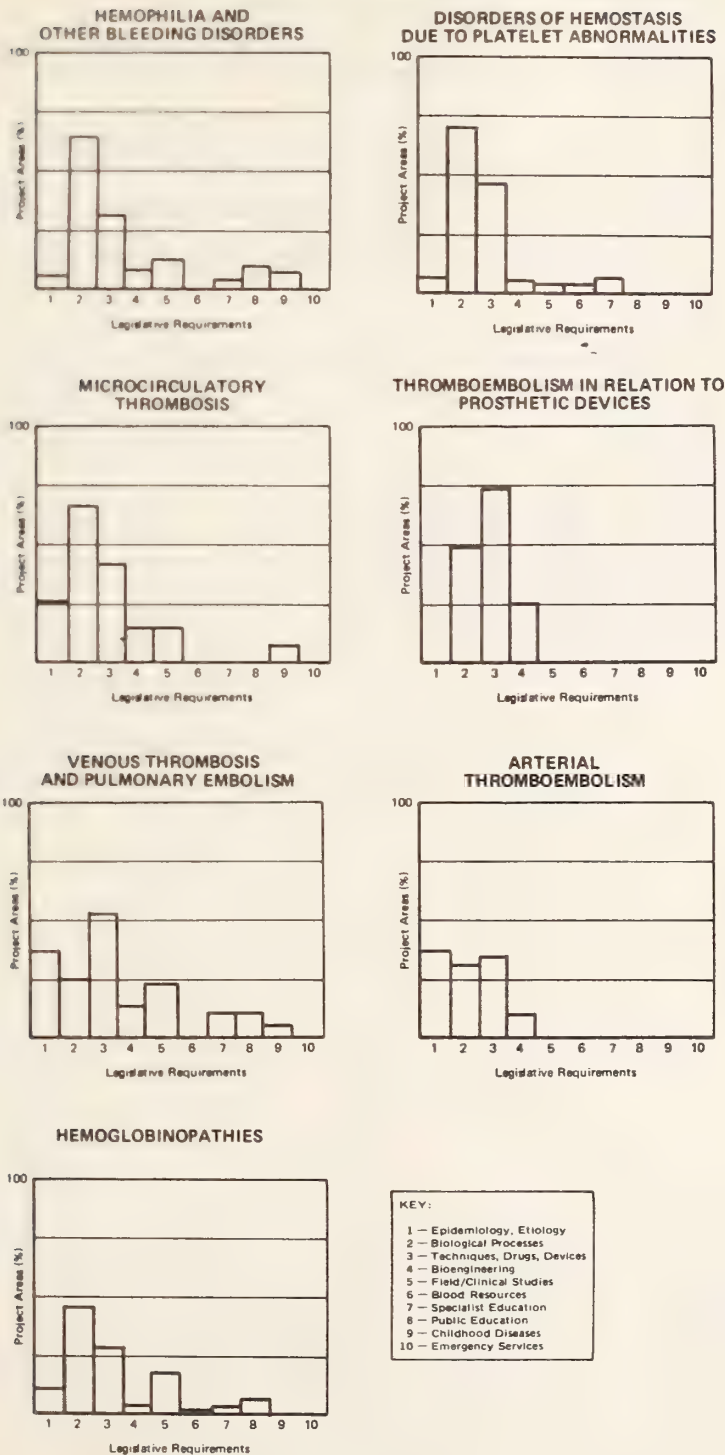


Figure B-2

INDIVIDUAL TASK GROUPS



2. Distribution of Project Areas with Respect to the Program Objectives

Table B-2 presents, on a task group basis, the percentage of project areas which relate to the four primary program objectives. The percentage distribution for all the task groups as a composite is shown in Figure B-3 and Figure B-4 presents the percentage distribution for each task group.

The four primary program objectives are:

- A. Prevention
- B. Detection and Diagnosis
- C. Treatment and Management
- D. Rehabilitation.



Table B-2

DISTRIBUTION OF PROJECT AREAS WITH RESPECT TO PROGRAM OBJECTIVES

Task Group	No. of Project Areas	Primary Program Objectives			
		A	B	C	D
Hemophilia and Other Bleeding Disorders	82	55%	68%	71%	16%
Disorders of Hemostasis Due to Platelet Abnormalities	55	65%	76%	71%	0
Microcirculatory Thrombosis	33	39%	61%	18%	0
Thromboembolism in Relation to Prosthetic Devices	43	63%	30%	7%	0
Venous Thrombosis and Pulmonary Embolism	55	56%	60%	44%	33%
Arterial Thromboembolism	38	89%	37%	39%	21%
Hemoglobinopathies	85	27%	44%	79%	7%
TOTAL	391	53%	55%	54%	12%

Figure B-3

COMPOSITE FOR ALL TASK GROUPS

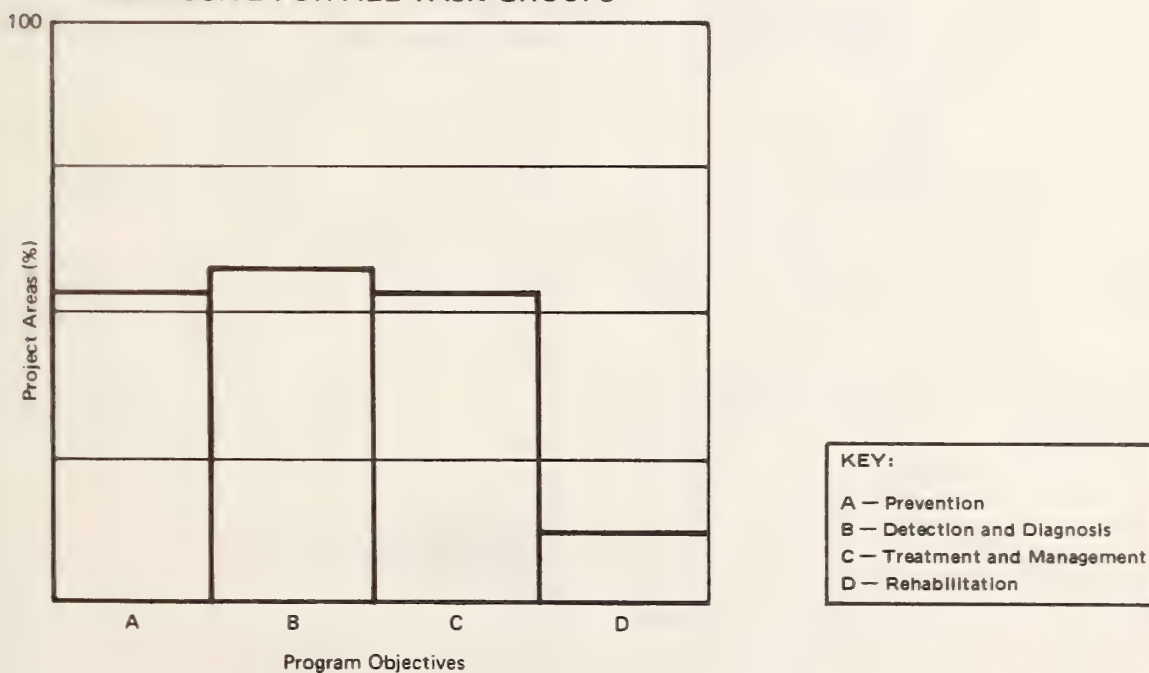
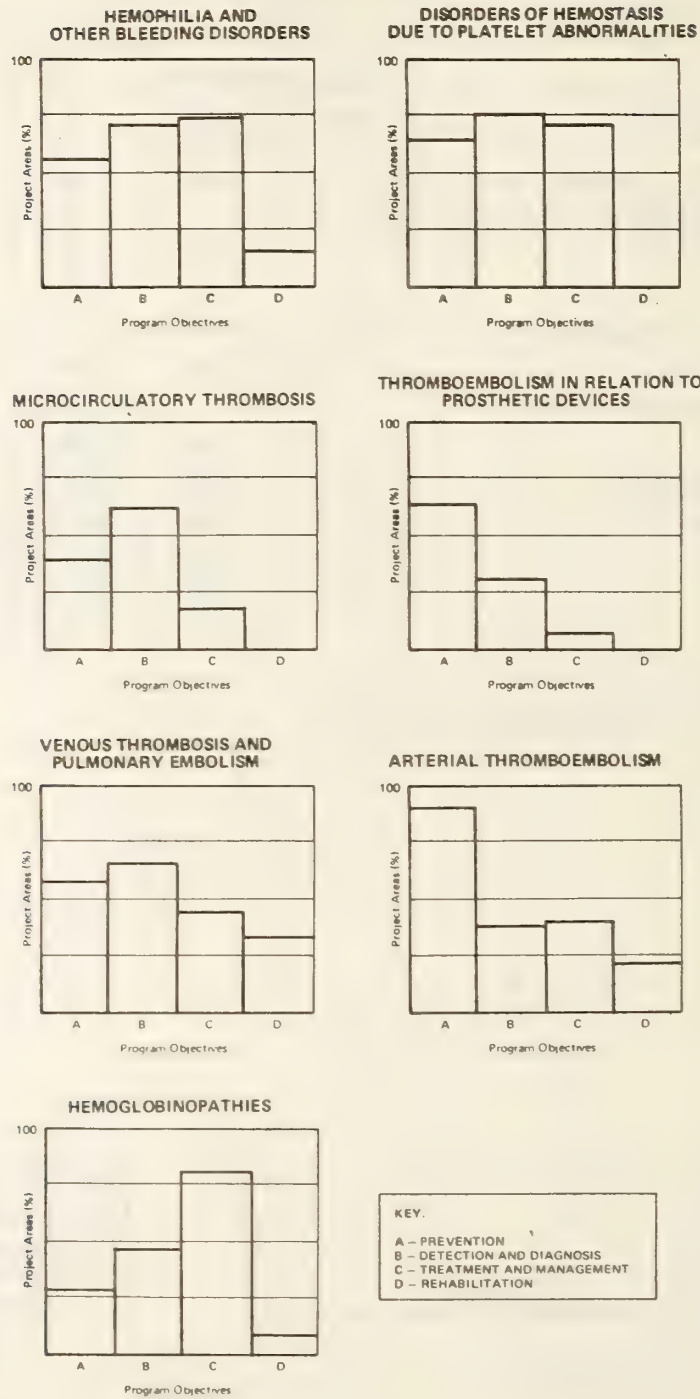


Figure B-4
INDIVIDUAL TASK GROUPS



APPENDIX C

DATA SUMMARY



APPENDIX C
DATA SUMMARY

This appendix provides a summary of the data base, i.e., the problems, approaches and project areas, which resulted from extensive deliberations of the seven Task Groups. A detailed discussion of each of these items is given in the individual Task Group materials.

The numbers of problems, approaches, and project areas identified by each Task Group are summarized in Table C-1. The listing which follows provides the corresponding titles for each category, ordered by number. The first digit identifies the problem, the second digit the approach, and the third digit the project area.



Table C-1
DATA SUMMARY FOR BLOOD DISEASES PANEL

No.	Task Group	Problems	Approaches	Project Areas
1	Hemophilia and Other Bleeding Disorders	8	18	82
2	Disorders of Hemostasis Due to Platelet Abnormalities	5	11	55
3	Microcirculatory Thrombosis	3	5	33
4	Thromboembolism in Relation to Prosthetic Devices	4	13	43
5	Venous Thrombosis and Pulmonary Embolism	3	19	55
6	Arterial Thromboembolism	1	11	38
7	Hemoglobinopathies	7	21	85
	TOTAL	31	98	391

DATA SUMMARY FOR
TASK GROUP 1

HEMOPHILIA AND OTHER BLEEDING DISORDERS



PROBLEM 1. HEMOPHILIA (HEREDITARY DEFICIENCIES OF FACTOR VIII AND FACTOR IX)

- 1.1 Prenatal Diagnosis of Hemophilia.
 - 1.1.1 Search for polymorphic genetic markers detectable in amniotic fluid linked to genes for factor VIII and factor IX.
 - 1.1.2 Development of methods for detection of the abnormal genetic material of factor VIII and factor IX deficiency in cultured amniotic fluid cells.
 - 1.1.3 Determination of gestational ages at which the plasma clotting factors are detectable in the fetus.
 - 1.1.4 Development of techniques for safe sampling of fetal blood at early gestational age.
- 1.2 Genetic and Abortion Counseling.
 - 1.2.1 Analysis of reasons for current failure of genetic counseling in hemophilia.
 - 1.2.2 Analysis of potential of abortion counseling for reducing incidence of hemophilia.
 - 1.2.3 Development of improved educational and communication techniques for counseling.
 - 1.2.4 Development of techniques for early sex determination of the fetus.
- 1.3 Genetic Engineering.
 - 1.3.1 Determine contribution of autosomal locus and X-chromosome locus to synthesis of factors VIII and IX.
- 1.4 Diagnosis of Carriers of Factor VIII and Factor IX Deficiency.
 - 1.4.1 Improved methodology for preparation of a pure heterologous antibody to pure factor VIII.
 - 1.4.2 Levels of CRM in carriers and hemophilia patients (factor VIII deficiency) as determined with antibody from Project Area 1.4.1.
 - 1.4.3 Comparison of factor VIII to CRM ratios in normals, carriers, hemophilic subjects, and patients with von Willebrand's disease utilizing pure heterologous antibody.
 - 1.4.4 Preparation of pure heterologous antibody to pure factor IX and its use in detection of carriers.
- 1.5 Replacement Therapy of Factor VIII and Factor IX Deficiency.
 - 1.5.1 Molecular characteristics of factor VIII in humans and animals.
 - 1.5.2 Molecular characteristics of factor IX in humans and animals.
 - 1.5.3 Determine the mechanisms of chemical function of factor VIII.
 - 1.5.4 Determine the mechanisms of chemical function of factor IX.
 - 1.5.5 Molecular characteristics of abnormal IX in PTC disease and vitamin K deficiency.
 - 1.5.6 Molecular characteristics of abnormal VIII in hemophilia and VW disease.
 - 1.5.7 Exploration of synthetic substitutes for chemical function of factors VIII and IX.
 - 1.5.8 Improved techniques for human factor VIII and factor IX concentrate production.
 - 1.5.9 Mechanisms of inactivation of factor VIII and factor IX.
 - 1.5.10 Mechanisms of activation of factors VIII and IX.
- 1.6 Prolongation of In Vivo Survival of Replacement Proteins.
 - 1.6.1 Establish mechanisms of normal catabolism of factors VIII and IX.
 - 1.6.2 Pharmacologic modification of catabolic rates of factors VIII and IX, in animals with



hereditary deficiencies of factor VIII and factor IX (regional veterinary centers for research on blood coagulation factors in animal model systems will be advocated in relation to this project).

- 1.7 Adjunctive Therapy in the Hemophilias.
 - 1.7.1 Use of antifibrinolytic agents as adjunctive therapy.
 - 1.7.2 Identification of drugs affecting stability of hemostatic plugs in hemophilic patients.
 - 1.7.3 Clinical evaluation of alternatives in management of acute joint hemorrhages hemophilia.
 - 1.7.4 Research in dental care techniques.
 - 1.7.5 Research in psychiatric management techniques.
 - 1.7.6 Studies of use in pharmacologic agents facilitating absorption of factors VIII and IX from intramuscular and subcutaneous sites in animals with hereditary factor VIII and factor IX deficiencies (veterinary centers needed also for this project).
- 1.8 Prevention and Management of Inhibitors in Patients with Hereditary Factor VIII Deficiency.
 - 1.8.1 Investigation of allotypes of factors VIII and IX.
 - 1.8.2 Identification of host factors leading to formation of inhibitors.
 - 1.8.3 Development of improved and standardized methodology for quantitation of inhibitors.
 - 1.8.4 Study of factor VIII antigen-inhibitor antibody interaction.
 - 1.8.5 Clinical trials of management protocols including protocols for the use of immuno-suppressive agents.
 - 1.8.6 Development of a protocol for determining inhibitor potential prior to elective surgery.
- 1.9 Tissue Transplantation in Hemophilia Therapy.
 - 1.9.1 Determination of site of synthesis of factor VIII.
 - 1.9.2 Mechanism of regulation of synthesis of factors VIII and IX (feedback, hormones von Willebrand factor, etc.).
 - 1.9.3 Evaluation of storage site of factors VIII and IX.
- 1.10 Integrated Rehabilitative Approach to Hemophilia: Physical, Psychological and Vocational.
 - 1.10.1 Regional center rehabilitative training programs: orthopedics, dentistry, psychiatry, vocational guidance, physical therapy.
 - 1.10.2 Controlled study of the value of selected orthopedic procedures in rehabilitation; e.g., synovectomy.
 - 1.10.3 Study of the influence of insurance and hiring policies on vocational rehabilitation in hemophilia.
- 1.11 Study of Value of Regional Centers for Clinical Research Training of Specialists, Education and Patients and Families in Home Care.
 - 1.11.1 Training of medical and paramedical personnel for hemophilia management: internists, pediatricians, orthopedic surgeons, physiotherapists, oral surgeons, psychiatrists and psychologists, pathologists and laboratory technologists.
 - 1.11.2 Education of hemophilia patient and family in all aspects of care including home care.
 - 1.11.3 Clinical research trials of new therapeutic modalities.
 - 1.11.4 Analysis of effectiveness of centers as diagnostic centers for bleeding diseases.



PROBLEM 2. DEFICIENCIES AND DISORDERS OF FACTORS II, VII, AND X

- 2.1 Elucidation of Structure, Function, Synthesis, and Catabolism of Factors II (Prothrombin), VII, and X.
 - 2.1.1 Isolation and characterization of factors II, VII, and X (including homology).
 - 2.1.2 Mechanisms of activation of factors II, VII and X including structure and role of tissue factor.
 - 2.1.3 Role of activated factors II, VII, and X in clotting process (including autocatalytic effects of thrombin).
 - 2.1.4 Mechanism of inactivation of activated forms of factors II, VII, and X.
 - 2.1.5 Sites, mechanisms, control of and role of Vitamin K and its antagonists in synthesis of these factors.
 - 2.1.6 Sites and mechanisms of catabolism of these factors.
 - 2.1.7 Molecular abnormalities associated with hereditary deficiencies of factors II, VII, and X.

PROBLEM 3. DISORDERS OF FIBRIN POLYMERIZATION AND CROSS-LINKING

- 3.1 Elucidation of Structure, Function, Synthesis, and Catabolism of Fibrinogen and Factor XIII.
 - 3.1.1 Analysis of polypeptide chain composition of human fibrinogen.
 - 3.1.2 Relation between hereditary structural aberrations of fibrinogen and abnormal function of the molecule.
 - 3.1.3 Determination of molecular events in the polymerization reaction, including role of factor XIII.
 - 3.1.4 Structure, activation, and function of factor XIII.
 - 3.1.5 Mechanism of normal catabolism of fibrinogen.
 - 3.1.6 Mechanism of normal catabolism of factor XIII.
 - 3.1.7 Determination of physiological and pathological regulation of fibrinogen synthesis.
 - 3.1.8 Determination of physiological and pathological regulation of factor XIII synthesis.

PROBLEM 4. HEREDITARY DEFICIENCIES OF FACTORS XI AND XII

- 4.1 Elucidation of Structure, Function, Synthesis and Catabolism of Factors XI and XII.
 - 4.1.1 Isolation and characterization of factors XI and XII.
 - 4.1.2 Mechanisms of activation of factors XI, XII, and Fletcher factor.
 - 4.1.3 Interaction of factor XII with processes other than coagulation: complement, fibrinolysis, and kinin systems.
 - 4.1.4 Mechanisms of inactivation of activated forms of factors XI and XII.
 - 4.1.5 Sites, mechanisms, and control of synthesis of factors XI and XII.
 - 4.1.6 Sites, mechanisms and control of catabolism of factors XI and XII.
 - 4.1.7 Molecular abnormalities associated with hereditary deficiency of factors XI and XII.

PROBLEM 5. HEREDITARY DEFICIENCY OF FACTOR V

- 5.1 Elucidation of Structure, Function, Synthesis and Catabolism of Factor V.

- 5.1.1 Isolation and characterization of factor V.
- 5.1.2 Role of factor V in coagulation process; activation and inactivation.
- 5.1.3 Site, mechanism, and control of synthesis of factor V.
- 5.1.4 Site, mechanism, and control and catabolism of factor V.
- 5.1.5 Molecular abnormalities associated with hereditary deficiency of factor V.

PROBLEM 6. ACQUIRED INHIBITORS OF COAGULATION FACTORS

- 6.1 Elucidation of Pathogenesis, Mechanism of Action, Turnover, and Clinical Management of These Acquired Inhibitors.
 - 6.1.1 Study of acquired factor VIII inhibitors in nonhemophilic patients: pathogenesis, mechanism of action, and clinical management.
 - 6.1.2 Study of acquired factor V inhibitors: pathogenesis, mechanisms of action, and clinical management.
 - 6.1.3 Study of acquired factor XIII inhibitors: pathogenesis, mechanism of action, and clinical management.
 - 6.1.4 Study of the prothrombin-activator inhibitor in lupus erythematosus: pathogenesis, mechanism of action and clinical management.

PROBLEM 7. ACQUIRED BLEEDING DISORDER OF LIVER DISEASE

- 7.1 Elucidation of Mechanisms and Study of Clinical Management of the Acquired Bleeding Disorder of Liver Disease.
 - 7.1.1 Study of the causes of impaired fibrin polymerization in liver disease.
 - 7.1.2 Identification of causes for coagulation factor deficiencies in liver disease: defective synthesis accelerated destruction due to clotting and fibrinolysis.
 - 7.1.3 Management of hemostatic defects during gastro-intestinal bleeding in liver disease.

PROBLEM 8. NONHEREDITARY BLEEDING DISORDERS OF THE NEWBORN

- 8.1 Elucidation of mechanisms and study of clinical management of nonhereditary bleeding disorders of the newborn.
 - 8.1.1 Study of etiology and mechanism of "hemorrhagic disease of the newborn."
 - 8.1.2 Study of clinical significance and mechanism of bleeding in the infected newborn.
 - 8.1.3 Role of vitamin K deficiency in bleeding of the newborn and during first six months of life—effect of synthetic diets, sterile food, infantile diarrhea.

DATA SUMMARY FOR
TASK GROUP 2

DISORDERS OF HEMOSTASIS
DUE TO PLATELET ABNORMALITIES



PROBLEM 1. BLEEDING DUE TO PLATELET DYSFUNCTION

- 1.1 Prevention of Platelet Defects which may be Associated with Clinical Bleeding Disorders.
 - 1.1.1 Prevention of drug-induced platelet defects.
 - 1.1.2 Treatment of acquired diseases in which platelet dysfunction may occur.
 - 1.1.3 Education of professionals in medicine regarding recent advances in the field and of potentiality for drug-induced platelet dysfunction.
- 1.2 Detection of Abnormalities of Platelet Function.
 - 1.2.1 Evaluation of platelet aggregation in whole blood.
 - 1.2.2 Evaluation of platelet function in patients with thrombocytopenia.
 - 1.2.3 Improved methods for studying platelet adhesion.
 - 1.2.4 Evaluation of platelet function tests—clinical correlation.
 - 1.2.5 Improved classification of disorders of platelet function.
 - 1.2.6 Development of clinically applicable screening tests.
 - 1.2.7 Education of physicians and laboratory directors in this area.
- 1.3 Treatment and Management of Bleeding due to Platelet Dysfunction.
 - 1.3.1 Discontinuation of offending drugs.
 - 1.3.2 Development of drugs which reverse platelet defects.
 - 1.3.3 Treatment of underlying, acquired diseases.
 - 1.3.4 Transfusion of platelets and other blood products.
- 1.4 Basic Research in Disorders of Platelet Function.
 - 1.4.1 Thrombasthenia.
 - 1.4.2 Abnormalities of the release reaction-storage pool diseases and other disorders.
 - 1.4.3 Von Willebrand's disease.
 - 1.4.4 Acquired platelet dysfunction.
 - 1.4.5 Establishment of special centers.

PROBLEM 2. THROMBOCYTOPENIA

- 2.1 Prevention of Thrombocytopenia.
 - 2.1.1 Drug-induced thrombocytopenia.
 - 2.1.2 Treatment of diseases in which thrombocytopenia may occur.
 - 2.1.3 Education of professional personnel.
- 2.2 Detection and Diagnosis of Thrombocytopenia.
 - 2.2.1 Incorporation of the platelet count into the routine blood count.
 - 2.2.2 Differentiation of destructive from productive defects.
 - 2.2.3 Detection of defects of production.
 - 2.2.4 Detection of increased platelet destruction.
- 2.3 Treatment and Management of Patients with Thrombocytopenia.
 - 2.3.1 Assessment of danger of bleeding.



- 2.3.2 Platelet transfusions.
- 2.3.3 Disorders of decreased platelet production.
- 2.3.4 Problems related to disorders due to increased platelet destruction.
- 2.4 Basic Research in Thrombocytopenia.
 - 2.4.1 Megakaryocyte studies.
 - 2.4.2 Hormonal control of platelet production.
 - 2.4.3 Studies on basic mechanisms of platelet destruction.
 - 2.4.4 Factors involved in platelet senescence.

PROBLEM 3. ROLE OF PLATELETS IN HEMOSTASIS

- 3.1 Basic Research on Platelet Function.
 - 3.1.1 Platelet ultrastructure.
 - 3.1.2 Plasma membrane studies.
 - 3.1.3 Mechanisms of platelet adhesion.
 - 3.1.4 Release reaction.
 - 3.1.5 Mechanism of platelet aggregation.
 - 3.1.6 Role of platelets in coagulation.
 - 3.1.7 Metabolic aspects of platelet behavior.
 - 3.1.8 Platelet proteins.

PROBLEM 4. OTHER (NONHEMOSTATIC) PROPERTIES

- 4.1 To Study Other (Nonhemostatic) Biological Properties of Platelets.
 - 4.1.1 Maintenance of endothelial integrity.
 - 4.1.2 Effect of platelet injury on vascular permeability.
 - 4.1.3 Role of platelets in immune reactions.
 - 4.1.4 Possible role of platelets in development of atherosclerosis.
 - 4.1.5 Role of platelets in microembolism.
 - 4.1.6 Role of vasoactive substances in platelets.
 - 4.1.7 Platelets in the host response to injury.
 - 4.1.8 Role of platelets in thrombosis.

PROBLEM 5. PLATELET PHARMACOLOGY

- 5.1 Basic Studies on the Effects of Drugs on Platelets.
 - 5.1.1 Mechanism by which drugs inhibit the release reaction.
 - 5.1.2 Mechanism by which drugs inhibit ADP-induced aggregation.
 - 5.1.3 Mechanism by which some drugs inhibit platelet reactivity in vivo.
 - 5.1.4 Mechanisms by which other types of drugs modify platelet behavior.
 - 5.1.5 Use of the platelet as a pharmacological model for study of other cells.



DATA SUMMARY FOR
TASK GROUP 3

MICROCIRCULATORY THROMBOSIS



PROBLEM 1. RECOGNITION OF DIC AND VASCULOPATHY SYNDROMES

- 1.1 Detection and Diagnosis of DIC and Vasculopathy Syndromes by Noninvasive Techniques.
 - 1.1.1 Development of sensitive and specific immunologic and biochemical methods of identification and quantification of coagulation factors, inhibitors, and platelet constituents.
 - 1.1.2 Development of sensitive and specific methods of identification and quantification of substances not ordinarily detectable in blood, such as endotoxins, thromboplastins, organisms, fibrinopeptides A and B and other substances.
 - 1.1.3 Specific identification and quantification of degradation products of fibrinogen and fibrin.
 - 1.1.4 Specific identification and quantification of the effects of plasmin and plasmin-like enzymes on polypeptides and other blood components.
 - 1.1.5 Development of methods for identification of the components of functionally interacting systems (e.g., kallikrein, complement).
 - 1.1.6 Development and refinement of specific methods for identification of thrombin or thrombin-like action on fibrinogen.
 - 1.1.7 Development and refinement of specific methods for identification of thrombin-like action on other blood components.
 - 1.1.8 Development of sensitive methods for detection of subtle forms of tissue and organ damage (e.g., tissue and organ products).
 - 1.1.9 Evaluation of the rheological characteristics of blood and blood components by in vitro methods.
 - 1.1.10 Evaluation of the rheological characteristics of blood and blood components in vivo.
- 1.2 Detection and Diagnosis of DIC and Vasculopathy Syndromes by Invasive Techniques.
 - 1.2.1 Development of sensitive and specific methods for distinguishing altered rates of turnover and for identification of metabolic intermediates.
 - 1.2.2 Development of sensitive methods for assessment of subtle organ damage manifested by alterations in perfusion (e.g., DIC involving kidneys).

PROBLEM 2. FACTORS CONTRIBUTING TO DIC

- 2.1 Pathophysiology of DIC.
 - 2.1.1 Identification of factors (e.g., endotoxins) causing endothelial damage and their resultant interaction with circulating blood components.
 - 2.1.2 Interaction of subendothelial components and circulating blood.
 - 2.1.3 Mechanisms of activation of factor XII and their consequences: mechanisms involving the initiation of coagulation, fibrinolytic, kallikrein and complement systems.
 - 2.1.4 The role of tissue thromboplastins in the initiation and propagation of DIC (release interaction with factor VII, subcellular localization, etc.).
 - 2.1.5 The role of blood cell injury (red cell, white cell, platelets) in initiation and propagation of DIC.
 - 2.1.6 Rheological factors in initiation and propagation of DIC.
 - 2.1.7 Effect of reticulo-endothelial and other clearance mechanisms on the perpetuation and acceleration of DIC.

- 2.1.8 Positive feedback mechanisms as accelerators of DIC.
- 2.1.9 Role of naturally occurring plasma proteolytic enzyme inhibitors in modulating DIC.
- 2.1.10 Other predisposing conditions to DIC; for example, the puerperium, drugs, etc.
- 2.1.11 Prospective studies of overall incidence and analysis of risk factors, such as predisposing disease states, drug therapy, pregnancy, physiological and psychological stress.
- 2.1.12 Identification of specific organ pathology as correlated with clinical risk factors and laboratory assessment.
- 2.2 Local and Generalized Vasculopathy.
 - 2.2.1 Detection and diagnosis of thrombosis as a component of allograft rejection.
 - 2.2.2 Investigation of relationship between generalized vasculopathy (i.e., virus, toxin, etc.).
 - 2.2.3 Identification of causative agents in generalized vasculopathy (i.e., virus, toxin, etc.).
 - 2.2.4 Identification of causative agents and/or host factors in localized vasculopathy of lung (e.g., hyaline membrane disease).
 - 2.2.5 Controlled studies of the role of antithrombotic agents and other therapeutic measures (i.e., immunosuppressive) in preventing or reducing organ damage.

PROBLEM 3. ANTITHROMBOTIC THERAPEUTIC MEASURES

- 3.1 Treatment and Mangement of DIC and Vasculopathy.
 - 3.1.1 Controlled clinical studies of antithrombotic versus supportive therapy; by early or preemptive treatment of DIC to decrease mortality and prevent organ damage.
 - 3.1.2 Controlled animal studies of pharmacologic and related substances in modification of vasculopathy or DIC.
 - 3.1.3 Antithrombotic therapeutic regimens in the modification of DIC and vasculopathy.
 - 3.1.4 Investigation and identification of exogenous agents which activate the fibrinolytic system.
 - 3.1.5 Treatment of hyaline membrane disease (HMD).

DATA SUMMARY FOR
TASK GROUP 4

THROMBOEMBOLISM IN RELATION
TO PROSTHETIC DEVICES



PROBLEM 1. MATERIALS FOR PROSTHETIC DEVICES

- 1.1 Development of Improved Material: A. Characterization of Material.
 - 1.1.1 Preparation of clean surfaces.
 - 1.1.2 Characterization of surface properties: Surface charge.
 - 1.1.3 Characterization of surface properties: Free energy.
 - 1.1.4 Characterization of surface properties: Texture.
 - 1.1.5 Characterization of surface properties: Induced structuring of water.
 - 1.1.6 Characterization of surface properties: Other properties.
 - 1.1.7 Stability of prosthetic materials in biologic systems.
 - 1.1.8 Characterization of bulk properties.
- 1.2 Development of Improved Material: B. Characterization of Reactions of the Blood to Surface Contact.
 - 1.2.1 Effects of blood-surface interaction on the surface: Analysis of the absorbed film of blood components.
 - 1.2.2 Effects of blood-surface interaction on the surface: Model systems for studying blood-surface interaction.
 - 1.2.3 Effects of blood-surface interaction on the blood: Nature and composition of "normal" blood, including variations among patients and in different species.
 - 1.2.4 Effects of blood-surface interaction on the blood: Effect of surface contact on formed elements.
 - 1.2.5 Effects of blood-surface interaction on the blood: Effect of surface contact on plasma components.
- 1.3 Development of Improved Material: C. Techniques for Passivation of Surfaces.
 - 1.3.1 Tissue induction techniques.
 - 1.3.2 Precoating with blood components.
- 1.4 Development of Improved Material: D. Preparation of Nonthrombogenic Material.
 - 1.4.1 Construction of nonthrombogenic materials.
 - 1.4.2 Evaluation of nonthrombogenic materials.

PROBLEM 2. IMPACT OF PROSTHETIC DEVICES ON RHEOLOGY

- 2.1 Improvements in Engineering and Design (Rheology of Thrombosis).
 - 2.1.1 Rheology of blood.
 - 2.1.2 Influence of flow conditions on thrombosis.
 - 2.1.3 Alterations in the rheology of blood in disease.
 - 2.1.4 Alterations in the rheology of blood produced by drugs.
- 2.2 Suppression of Thromboembolism in Relation to Prosthetic Devices by the Administration of Drugs.
 - 2.2.1 Anticoagulants.
 - 2.2.2 Agents affecting platelet function.
 - 2.2.3 Thrombolytic agents.

- 2.2.4 Drugs bonded to surfaces.
- 2.3 Blood Filtration.
 - 2.3.1 Pathophysiology of particulate material in the blood.
 - 2.3.2 Improved blood filters.

PROBLEM 3. BLOOD-SURFACE INTERACTIONS

- 3.1 In Vivo Methods for Detection of Blood-Surface Interactions: A. Effects on the Device.
 - 3.1.1 Detection of thrombotic deposits on prosthetic surfaces.
 - 3.1.2 Functional assessment of devices.
- 3.2 In Vivo Methods for Detection fo Blood-Surface Interaction: B. Effects on the Blood.
 - 3.2.1 Determination of the survival of blood components.
 - 3.2.2 Detection of alterations in and consumption of blood components.
 - 3.2.3 Detection of microembolism.
 - 3.2.4 Detecñon of alterations in red cells.
- 3.3 In Vivo Methods for Detection of Blood-Surface Interaction: C. Remote Effects on Organ Function.
 - 3.3.1 Microembolism.
 - 3.3.2 Hemorrhage.
 - 3.3.3 Effects of circulating blood components.
- 3.4 In Vitro Methods for Characterization of Blood-Surface Interactions.
 - 3.4.1 Surface induced alterations in platelets.
 - 3.4.2 Surface induced alterations in plasma components.
 - 3.4.3 Surface induced alterations in red cells and white cells.
 - 3.4.4 In Vitro models.

PROBLEM 4. THERAPEUTIC MEASURES

- 4.1 Drug Therapy.
 - 4.1.1 Thrombolytic agents.
- 4.2 Replacement Therapy.
 - 4.2.1 Basic studies in replacement therapy with blood components, detailed elsewhere in this report.
 - 4.2.2 Basic studies in the physiology of hemostasis, detailed elsewhere in this report.

DATA SUMMARY FOR
TASK GROUP 5

VENOUS THROMBOSIS AND PULMONARY EMBOLISM



PROBLEM 1. BLAND VENOUS THROMBOEMBOLISM

- 1.1 Definition of Prevalence of Venous Thrombosis and Pulmonary Embolism in Defined Patient Subgroups.
 - 1.1.1 Prevalence of venous thrombosis and pulmonary embolism in patients undergoing thoracotomy.
 - 1.1.2 Prevalence of V.T. and P.E. in patients undergoing laparotomy.
 - 1.1.3 Prevalence of V.T. and P.E. in all patients coming to autopsy at a given institution.
 - 1.1.4 Establishment of autopsy criteria for diagnosis of V.T. and P.E.
- 1.2 Protection of Defined Populations.
 - 1.2.1 Clinical trials of antithrombotic agents on defined populations.
- 1.3 Education of Populations at Risk.
 - 1.3.1 Prolonged air travel.
 - 1.3.2 Prolonged surface travel.
- 1.4 Physician Education.
 - 1.4.1 Education concerning V.T. and P.E. risk factors.
- 1.5 Pathogenesis of Venous Thrombosis.
 - 1.5.1 Isolation and characterization of components involved in the early stages of coagulation.
 - 1.5.2 Induction of venous thrombosis in animal models.
 - 1.5.3 Study of patients with known thrombotic tendency.
 - 1.5.4 Study of autopsy material.
 - 1.5.5 Study of the effects of endotoxin and immune complexes.
- 1.6 Blood Tests for Thrombotic Tendency.
 - 1.6.1 Study of existing procedures.
 - 1.6.2 Development of new procedures.
- 1.7 Education—Training of Personnel.
 - 1.7.1 Training programs.
 - 1.7.2 Support of nonphysician research personnel.
- 1.8 Physician Education, Diagnostic.
 - 1.8.1 Education concerning techniques in diagnosis of V.T. and P.E.
- 1.9 Development of Noninvasive Diagnostic Techniques.
 - 1.9.1 ¹²⁵I-fibrinogen.
 - 1.9.2 Impedance devices.
 - 1.9.3 Ultrasound (Doppler) method.
 - 1.9.4 Ventilation/perfusion scintiphotography.
 - 1.9.5 Videodensitometry.
- 1.10 Invasive Diagnostic Techniques.
 - 1.10.1 Venography.
 - 1.10.2 Pulmonary angiography.
 - 1.10.3 Improved angiographic venographic media (contrast materials).



- 1.11 Blood Tests for Detecting Venous Thrombosis.
 - 1.11.1 Study of existing approaches.
 - 1.11.2 Study of fibrin and fibrinogen degradation products.
 - 1.11.3 Study of interaction fibrinogen, fibrin and fibrin degradation products with potential labeling materials.
 - 1.11.4 Study of other materials incorporated into venous thrombi.
- 1.12 Medical (Drug) Therapy.
 - 1.12.1 Heparin dosage regimens.
 - 1.12.2 Prothrombinopenic agents.
 - 1.12.3 Thrombolytic agents.
 - 1.12.4 Defibrinating agents, dextran, antiplatelet agents.
 - 1.12.5 Development of oral heparin.
- 1.13 Surgical Therapy.
 - 1.13.1 Venous ligation-plication procedures.
 - 1.13.2 Acute embolectomy.
 - 1.13.3 Trans-venous interruptive devices.
- 1.14 Natural History of Venous Thrombosis and Pulmonary Embolism.
 - 1.14.1 Natural history of venous thrombi.
 - 1.14.2 Thrombi as sources of emboli.
 - 1.14.3 Natural history of pulmonary emboli.
 - 1.14.4 Humoral/reflex mechanisms in acute embolism.
 - 1.14.5 Dyspnea in embolism.
 - 1.14.6 Radiographic correlates of embolism.
 - 1.14.7 Pulmonary edema and embolism.
 - 1.14.8 Determinants of mortality in acute embolism.
- 1.15 Job Selection in Patients with a History of V.T. and P.E.
 - 1.15.1 Criteria for job selection.
 - 1.15.2 Insurability.
- 1.16 Criteria for Thromboendarterectomy.
 - 1.16.1 Segmental nature of chronic occlusion.
 - 1.16.2 Criteria for selection and technical considerations.

PROBLEM 2. SEPTIC PULMONARY EMBOLISM

- 2.1 Education of Population and Physicians.
 - 2.1.1 Drug abuse education.
 - 2.1.2 Ob-gyn physician education.
- 2.2 Therapy of Septic Embolism.
 - 2.1.1 Clinical therapeutic trials.



PROBLEM 3. FAT EMBOLISM

3.1 Conference.

3.1.1 Conference.

DATA SUMMARY FOR
TASK GROUP 6

ARTERIAL THROMBOEMBOLISM



PROBLEM 1. ARTERIAL THROMBOEMBOLISM

- 1.1 Relation of Thrombosis to Atherosclerosis.
 - 1.1.1 Improving dating of age of thrombi.
 - 1.1.2 Development of automated serial section techniques for study of arteries.
 - 1.1.3 Improved dating of age of infarcts.
 - 1.1.4 Animal models.
- 1.2 Recognition of Hypercoagulability.
 - 1.2.1 Analysis of platelet anatomy, physiology, and biochemistry.
 - 1.2.2 Appearance of breakdown products of clotting factors.
 - 1.2.3 Depression of normal clotting factor inhibitors.
- 1.3 Clinical Trials.
 - 1.3.1 Education of physicians and other scientists using clinical trials; training of biostatisticians interested in problems of clinical trials.
 - 1.3.2 Development of new statistical techniques.
- 1.4 Removal of Factors Predisposing to Thrombosis.
 - 1.4.1 Atherosclerosis.
 - 1.4.2 Rheumatic fever.
 - 1.4.3 Chronic arrhythmias.
 - 1.4.4 Congestive heart failure.
 - 1.4.5 Hypotension.
 - 1.4.6 Arterial wall injury.
 - 1.4.7 Vascular prosthesis.
 - 1.4.8 Angitis.
 - 1.4.9 Platelet disorders.
 - 1.4.10 Estrogen.
- 1.5 Prophylaxis of Arterial Embolism.
 - 1.5.1 Coumarin prophylaxis.
 - 1.5.2 Heparin prophylaxis.
 - 1.5.3 Antiplatelet aggregants.
- 1.6 Prophylaxis of Arterial Thrombosis.
 - 1.6.1 Coumarin prophylaxis.
 - 1.6.2 Heparin prophylaxis.
 - 1.6.3 Antiplatelet Aggregants.
 - 1.6.4 Thrombolytic prophylaxis.
 - 1.6.5 Venom prophylaxis.
- 1.7 Detection and Diagnosis of Arterial Thrombi.
 - 1.7.1 Invasive techniques: Holography combined with arteriography.
 - 1.7.2 Noninvasive techniques: Isotopes.



- 1.7.3 Noninvasive techniques: Ultrasound.
- 1.8 Treatment of Coronary Artery Thrombosis.
(See Approach 1.5 and 1.6.)
(See Panel on Heart and Blood Vessel Disease: Task Group 2 on Coronary Heart Disease.)
- 1.9 Treatment of Cerebrovascular Thrombosis.
(See Approach 1.5 and 1.6.)
(See Panel on Heart and Blood Vessel Disease: Task Group 5 on Stroke.)
- 1.10 Rehabilitation after Arterial Thromboembolism.
- 1.11 Basic Research in Clotting.
 - 1.11.1 Relation of lipids to blood coagulation.
 - 1.11.2 Activation of a clotting factor.
 - 1.11.3 Depression of normal clotting factor inhibitors.
 - 1.11.4 Studies in fibrinolysis.
 - 1.11.5 Snake venoms.
 - 1.11.6 Estrogens.
 - 1.11.7 Relation of clotting system to other protein systems.
 - 1.11.8 Heparin and coumarin drugs.
 - 1.11.9 Platelets (see Task Group on Disorders of Hemostasis).
 - 1.11.10 Vessel wall (see Task Group on Microcirculatory Thrombosis).



DATA SUMMARY FOR
TASK GROUP 7

HEMOGLOBINOPATHIES



PROBLEM 1. SICKLE CELL ANEMIA AND SICKLE CELL TRAIT

- 1.1 Structure and Formation of Polymers of Sickle Cell Hemoglobin.
 - 1.1.1 "Morphologic" evidence about deoxy Hb polymers, electron microscopy, X-ray diffraction.
 - 1.1.2 Mechanisms of reaction of polymerization.
 - 1.1.3 Participation of mutant and modified Hb S.
 - 1.1.4 Conditions or reagents which favor or impair polymerization.
 - 1.1.5 Development of methodology to follow polymerization—calorimetry, gelation, viscosity.
- 1.2 Pathogenesis of Vasocclusive Crises.
 - 1.2.1 Studies of the "physiologic state" of sicklers in the steady state and during crises.
 - 1.2.2 Studies of the red cells before and during and after crisis.
 - 1.2.3 Studies of the relationships of environmental changes, e.g., infections, on crisis.
 - 1.2.4 Development of a scale to indicate severity of crises.
 - 1.2.5 Nature of irreversibly sickled cells.
- 1.3 Management of Complications of Sickle Cell Disease.
 - 1.3.1 Management of chronic secondary complications including: ocular complications, cholelithiasis, renal dysfunction, leg ulcers, hepatic dysfunction, cardiac failure, bone infarcts, infections, dactylitis.
 - 1.3.2 Management of sickle cell disease in pregnancy.
 - 1.3.3 Management of vasocclusive crises.
- 1.4 The Effect of Sickle Cell Trait on Life Expectancy or on Morbidity.
 - 1.4.1 Epidemiologic studies—association of sickle trait with other diseases, and ages at death of sicklers and nonsicklers with same diseases—VA study.
 - 1.4.2 Epidemiologic studies—occurrence of other disorders in individuals with sickle trait on prospective basis—Armed Forces.
 - 1.4.3 Prospective study of a stable community (depending on cost).
 - 1.4.4 Physiological studies of sicklers and normals—effects of exercise, water deprivation, etc., studies of rhabdomyolysis.
 - 1.4.5 Influence of estrogen administration and pregnancy on women with sickle cell trait.
 - 1.4.6 Studies of effects of anesthesia and of pulmonary disease on individuals with sickle cell trait.
 - 1.4.7 Observations on the environmental effects on the manifestations of sickle cell trait in countries other than the USA.
- 1.5 Educational Programs.
 - 1.5.1 Educational programs for general public.
 - 1.5.2 Educational programs for specific population groups.
 - 1.5.3 Development of educational programs by community groups.
 - 1.5.4 Education of health professionals.
 - 1.5.5 Development of a training program for educational counselors for sickle cell disease and sickle cell trait.



- 1.5.6 Training of medical technologists, and other allied health professionals
- 1.6 Psychosocial Aspects of Sickle Cell Programs.
 - 1.6.1 Psychological effects on individuals.
 - 1.6.2 Psychological and sociologic effects on families with hemoglobin S.
 - 1.6.3 Psychosocial effects on black, brown and other subpopulations with hemoglobin S and on the white community.
- 1.7 Rehabilitation Centers.
 - 1.7.1 Medical rehabilitation.
 - 1.7.2 Vocational guidelines and training.
- 1.8 Evaluation of Education and Screening Programs.
 - 1.8.1 Follow-up population reached by education and screening programs.
 - 1.8.2 Use of statistical methods in evaluation of education and screening programs.

PROBLEM 2. Hb VARIANTS WHICH INTERACT WITH Hb S

- 2.1 Hemoglobins Interacting with Hb S.
 - 2.1.1 Studies of the clinical states associated with the presence of hemoglobin S and Hb variant.
 - 2.1.2 Studies of the properties of red blood cells containing Hb S and an Hb variant.
 - 2.1.3 Studies of the interactions of Hb variants and Hb S.
 - 2.1.4 Detection of and establishment of primary structure of Hb variants.
 - 2.1.5 Studies of the properties of isolated Hb C and Hb C in red cells.

PROBLEM 3. HEMOGLOBIN VARIANTS OTHER THAN Hb S

- 3.1 Hemoglobins with Altered Oxygen Affinity.
 - 3.1.1 Improved techniques for screening for hemoglobins of abnormal O₂ affinity.
 - 3.1.2 Support of laboratories for establishing primary structure.
 - 3.1.3 Measurement of physiological effects of abnormal O₂ release.
 - 3.1.4 Studies of the structure function relationships in these variants.
- 3.2 Pathogenesis of Hemolytic Anemia Associated with Unstable Hemoglobins.
 - 3.2.1 Ascertain primary structure of Hb variants.
 - 3.2.2 Studies of functional and structural relationships in unstable hemoglobins.
 - 3.2.3 Studies of effects of heme loss on hemoglobin synthesis and functions.
 - 3.2.4 Studies of fate of unstable Hb in cells and effects on red cell membranes.
 - 3.2.5 Studies of heme metabolism in normal and in unstable hemoglobins.
 - 3.2.6 Clinical studies of the effects of drugs and of splenectomy in these disorders.



PROBLEM 4. THALASSEMIA

- 4.1 Continuing Development of New Knowledge of Genetics and Molecular Biology to Indicate Avenues of Therapy for Thalassemia.
 - 4.1.1 An approach to the therapy of genetic disorders: specific genetic therapy in thalassemia.
 - 4.1.2 Transcriptional control of α/β imbalance.
 - 4.1.3 Translational control of α/β imbalance.
 - 4.1.4 Control of gamma to beta switch: mechanisms of gene switching.
 - 4.1.5 Intrauterine diagnosis in thalassemia.
- 4.2 Optimum Treatment of Thalassemia Major.
 - 4.2.1 Optimum transfusion program.
 - 4.2.2 Improved technology in blood banking and transfusion.
 - 4.2.3 Development of new effective chelators for iron.
 - 4.2.4 Studies of iron metabolism in normals and in iron overload.
- 4.3 Screening and Counseling Programs.
 - 4.3.1 Development of better techniques for identification of thalassemia heterozygotes.
 - 4.3.2 Social studies of mating patterns of Mediterranean immigrants and their descendants.
 - 4.3.3 Pilot studies to establish frequency of thalassemia trait in subjects of Mediterranean or African ancestry.
 - 4.3.4 Registration of the diagnosis of thalassemia major.
 - 4.3.5 Counseling and education programs in thalassemia.
 - 4.3.6 Identification of thalassemia in sickle screening programs.

PROBLEM 5. IMMUNOLOGY

- 5.1 Immunologic Techniques in Studies of Hemoglobin Diseases.
 - 5.1.1 Immunologic identification of hemoglobin variants detected electrophoretically.
 - 5.1.2 Immunologic studies of erythrocytes in thalassemia.
 - 5.1.3 Immunologic studies of hemoglobins of mild and severe sicklers.
 - 5.1.4 Immunologic studies of hemoglobin variants not detectable electrophoretically.

PROBLEM 6. RED CELL ENZYME DISORDERS

- 6.1 Control Mechanisms of Red Cell Glucose Metabolism.
 - 6.1.1 Development of methods for measurement of metabolic intermediates.
 - 6.1.2 Development of techniques for purification of red cell enzymes.
 - 6.1.3 Development of computerized models to predict alterations in steady state levels of intermediates.
- 6.2 Studies of the Cause of Red Cell Senescence and Premature Death.
 - 6.2.1 Red cell enzymes in blood stored in vitro and different ages of cell in vivo.
 - 6.2.2 Changes in conformation or chemical modification of red cell enzymes in old red cells.
 - 6.2.3 Localization (ultrastructure) of enzymes within red cells.



- 6.3 **Manipulation of Red Cell Metabolism by Environmental Agents.**
 - 6.3.1 Effect of environmental agents on activities of red cell enzymes.
 - 6.3.2 Control of 2, 3-DPG levels.
- 6.4 **Clinical Studies of Red Cell Metabolic Defects.**
 - 6.4.1 Development of better screening tests.
 - 6.4.2 Development of methods for measuring functional defects when there is no decrease in activity under usual assay conditions.
 - 6.4.3 Development and maintenance of a few sophisticated facilities for evaluation of unusual clinical cases.
 - 6.4.4 Development of better electrophoretic techniques for red cell enzymes.
- 6.5 **Studies of Enzyme Structure-Function Relationships.**
 - 6.5.1 Studies of primary structure of red cell enzyme variants.
 - 6.5.2 Studies of the function, e.g., Michaelis constants, allosteric interactions, thermostability of enzyme variants.
 - 6.5.3 X-ray crystallography, ultrastructure of red cell enzyme variants.

PROBLEM 7. RED CELL MEMBRANE DEFECTS

- 7.1 **Structure and Function of Red Cell Membranes.**
 - 7.1.1 Biochemical structure of red cell membranes.
 - 7.1.2 Ultrastructure of red cell membrane.
 - 7.1.3 Functional properties of red cell membrane—methods of measurement.
 - 7.1.4 Interactions of other components of red cell and red cell membranes.



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NATIONAL HEART, BLOOD VESSEL, LUNG AND BLOOD PROGRAM

VOLUME IV PANEL REPORTS

PART IV

REPORT OF THE BLOOD RESOURCES PANEL



APRIL 6, 1973

**U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
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F O R E W O R D

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 (Public Law 92-423) requires that the National Heart and Lung Institute develop a plan for a National Heart, Blood Vessel, Lung and Blood Disease Program. The Institute established a committee of four panels to assist in the development of program plans for each of the four major program areas:

- Heart and Blood Vessel Diseases
- Lung Diseases
- Blood Diseases
- Blood Resources.

This report was prepared by the Blood Resources Panel.

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P R E F A C E

The Ninety-Second Congress enacted the National Heart, Blood Vessel, Lung and Blood Act of 1972 (Public Law 92-423) to plan and target the attack on these major national problems. A Blood Resources and Transplantation Panel, consisting of eight (8) professionals representing various interests and disciplines concerned with the problems of blood resources and transplantation was appointed to prepare this plan. Members of the Panel served as chairmen for six (6) Task Groups appointed to consider specific problem areas of blood resources and transplantation. The total membership of the Blood Resources and Transplantation Task Group was 52 including the chairmen. Participants varied from blood bank administration to laboratory basic science, to clinical investigation, to the practice of medicine or surgery; and 43 medical centers in 20 states were represented (See Appendix A).

The several Task Group meetings produced scientific summary data, the basic information components from which this report was constructed. The fundamental structural unit was an approach to a particular problem; each approach was supplemented by component project area descriptions which outlined the steps to be employed to attain a specific objective. The scientific summary materials of each Task Group were reviewed by other members of the Task Group, with corrections and additions incorporated into subsequent drafts.



Each Task Group Chairman then synthesized the scientific data into a narrative summary. Suggestions for modifications of this summary were solicited from each Task Group member and incorporated into a subsequent summary; therefore, the narrative summaries and recommendations for each problem area represent a synthesis of Task Group effort. The narrative summaries prepared by the Task Groups were edited and condensed by the Panel Chairmen for inclusion here in the Panel report. Each Panel member had the opportunity to review and modify the edited version of this narrative summary.

The Panel report is subdivided into four major parts: Part I, which contains an introduction and general considerations; Part II, which discusses the problems and proposed programs for blood resources and transplantation; Part III, which is a summary of Panel recommendations; and Part IV, which relates the legislation requirements to the proposed program.



PART I

INTRODUCTION AND GENERAL CONSIDERATIONS



PART I
INTRODUCTION AND GENERAL CONSIDERATIONS

Large-scale blood transfusion and successful organ transplantation are both phenomena of the past 25 years. They represent major therapeutic advances which, though originating separately, have much in common. Their genetic and immunologic principles are similar, as are their related problems in ethics, human motivation, and social organization. To be optimally effective, both require a unique combination of human resources and scientific and medical expertise, and there is growing awareness that it is reasonable to consider them together in the formulation of nationwide goals and plans. Blood transfusion being the older and more widespread will be considered first. Approximately 9 million units¹ of blood and 1.7 million liters² of plasma were collected in the U.S. during

¹A unit of blood is 450 ml $\pm$ 10 percent or about one pint.

²A liter of plasma is the plasma equivalent obtained from 5 units of blood.



1971, probably more per capita than in any other country of the world. Despite this vast amount of resource material, there has been mounting public dissatisfaction, sometimes strident, with some aspects of the blood transfusion complex. It has been characterized as a fragmented patchwork, inadequately regulated and essentially unplanned; it has been criticized for being wasteful, overly commercialized, and relying too heavily on the underprivileged for much of its basic materials; it has been plagued by a widely disparate array of confusing charges; and it has suffered from an inadequate scientific base. Though appreciating the serious shortcomings in the existing system, the Panel recognizes that it also has many strengths, and that in the main it has served the American people well. The need for immediate future is to define clearly the nationwide goals and, utilizing existing resources whenever possible, to improve and expand the system.



The program goals for the best use of the nation's blood resources are, broadly stated, as follows:

- Development of an integrated and efficiently managed system to provide for all of the country's blood needs, including blood components and blood derivatives
- Materials and services in transfusion therapy to be of the highest quality and to meet uniformly high standards
- Essential transfusion materials and services to be available to all on the basis of need and at reasonable cost
- Expansion of the scientific base and training facilities (medical, technical, and administrative) to generate the new ideas and to furnish the manpower for optimal transfusion therapy.



The blood transfusion complex of this country may be conveniently divided into two parts: one part dealing with the supply of materials and services, and the other dealing with the utilization of these materials and services in the care of patients. The former, the supply element, consists of not-for-profit regional and community blood centers, commercial blood banks, some hospitals, and the pharmaceutical industry; the latter--the utilization or clinical arm of the system--is provided largely by hospitals and to a small extent by physicians in their offices or, in the case of hemophilia, in the home. Operationally there is some overlap between the two: the regional and community blood centers are often concerned with the care of individual patients at the bedside level, and hospitals collect a small but significant portion of the total blood supply (some 10 to 20 percent). For purposes of this part of the presentation, attention will be focused exclusively on the supply side of the picture. This is not in any way intended to minimize the essential role of the clinical transfusion services, which will be considered in connection with the research, development, and training programs.

It is the opinion of the Panel that there are several basic principles which should serve as the critical guidelines for the planned evolution of an effective blood program for the nation. These will be discussed individually in the sections to follow.



1.2.1 Voluntarism

There can be no question that the American people wish to have a totally volunteered blood supply. Buying and selling human blood, just as buying and selling human organs for transplantation, is no longer socially acceptable; this has become the operating principle of the major national blood organizations. It is entirely possible that, given a coordinated national effort, the goal of a completely voluntary blood supply can be attained within 2 to 3 years.

There are financial, medical, and social reasons for preferring voluntary blood donors. Costs associated with recruiting them are substantially lower than the fees paid to professionals. The cost differential between a 100 percent voluntary blood supply for the nation and one derived entirely from paid donors would be between \$40 million and \$100 million per year, a not insignificant sum.

It has been clearly demonstrated that blood from paid donors carries with it a three to tenfold higher risk of hepatitis. Indeed, it has been estimated that a totally voluntary blood supply would do more to reduce the incidence of post-transfusion hepatitis than the introduction of the best currently available test for detection of the hepatitis virus. This increased safety is perhaps the most widely cited reason for preferring voluntary blood. On the other hand, this argument would disappear should a more effective test for hepatitis be introduced, as now seems possible. Would paid blood donors be acceptable under those circumstances?



The Panel, recognizing the merits of the lowered cost and increased safety of voluntarily donated blood, is of the opinion that an even more cogent reason for preferring voluntarism is the ethical one. It is important, as noted by Professor Titmuss, to encourage every opportunity for altruism. A society which cherishes the worth of the individual and fosters a high sense of social responsibility cannot set a price on human organs and tissues. Giving blood is regarded as a much needed manifestation of man's humanity to man, to be fostered quite apart from any financial or medical advantages.

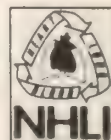
Probing deeper into the concept of voluntarism, however, raises troublesome questions to be faced realistically. The pharmaceutical industry collects 1.7 million liters of plasma each year for the manufacture of albumin, gamma globulin, specific immune globulins and a variety of diagnostic reagents. Almost all of this plasma is obtained by plasmapheresis from paid donors, much of it from penal institutions and decadent areas of our large cities, and some of it imported from underprivileged countries. Plasma, like blood and organs for transplantation, is a material that can be derived only from human beings, and its medical uses are of comparable importance. We stress the social values inherent in volunteering blood but accept, apparently without question, the purchase of plasma. This is a moral dilemma that should be either accepted or resolved.

The problem is further complicated by the fact that a significant portion of the plasma supply is used to prepare specific immune globulins and comes from donors who are hyperimmunized, naturally or more often deliberately.



Even if it were possible to supply all of our plasma needs from salvaged plasma or from volunteer plasmapheresis donors, is it likely that enough individuals will freely submit to hyperimmunization, a procedure whose eventual sequelae are still uncertain, as well as to regular plasmapheresis? And what of donors with particularly rare bloods, or the growing need for repetitive cytophoresis from HL-A matched donors for platelets or granulocytes? Is it reasonable to expect volunteers for these repetitive and time-consuming procedures?

There are those who feel strongly that all human products, even those requiring far greater personal sacrifice than that entailed in a single blood donation, should and can be obtained from volunteers. Others feel that this is unrealistic and that to try to do so would seriously jeopardize the source of essential therapeutic agents. It is interesting that representatives of the pharmaceutical industry have indicated willingness to give up their paid plasmapheresis centers if assured of a stable and adequate supply of voluntarily donated plasma. The Panel members are of the opinion that it would be desirable to obtain all human products voluntarily, even those requiring plasmapheresis, antigenic stimulation, or cytophoresis. Whether this is attainable without hazard to the current supply of these materials remains to be determined. The movement toward total voluntarism therefore must be tempered with caution, and preceded by carefully documented studies as to its feasibility and the possibility of developing socially acceptable, nonexploitive methods for compensating special donors. In the last analysis, society must determine the value it places on the volunteer principle and the sacrifices it is willing to make for it.



1.2.2 Regionalism

The American blood supply presently comes from a congeries of several thousand large and small hospital and community blood banks. This heterogeneous and essentially unplanned system is expensive and inefficient in its use of blood and of trained, medical, technical, and managerial personnel. It should gradually be replaced by a coordinated nationwide network of blood centers serving regions of the country rather than individual hospitals, small communities, or portions of a large city.

Regional blood centers are the logical functional unit of the nation's blood bank complex. Their larger size would permit them to take advantage of the economies of scale both professionally and administratively. Each regional blood center would develop a single comprehensive donor program to meet the needs of its area in place of the confusing and often conflicting array that now exists, and it would make more effective use of the communications media and other available community resources. The concept of regionalism in blood services is also consistent with the trend in other aspects of health care.

There is no simple formula for defining a region that meets all the needs and fits all the situations in a large and heterogeneous country, and there are different ways in which existing intraregional activities can be brought together to form an effective regional unit. This will clearly require patience, careful planning, and a spirit of cooperation. In general, subject to more precise demographic definition, a region should consist of a major urban area and the total



population of the surrounding area that relates to it naturally in terms of the transportation, industry, shopping, medical care, entertainment, etc. A regional center should be large enough to afford at least one full-time trained medical director, which suggests that it would serve a population of no less than one million people and draw at least 50,000 units of blood annually. By this crude rule of thumb, it is estimated that between 100 and 200 regional blood centers would be adequate for the whole country.

A regional blood center, having complete responsibility for furnishing an essential health service, is in many ways analogous to a public utility. As such, it must be publicly accountable for its professional activities, its management of the blood resources, and its finances. Its operations must be open to public scrutiny and its performance must meet the high standards set by a federal regulatory agency. The development and implementation of the regional concept in blood banking can be facilitated by appropriate management studies.

The regional blood centers are envisioned as more than large warehouses for blood. They need to be brought into the mainstream of medicine and science. They should, at minimum, accept total responsibility for all blood, blood components, and blood services required by patients in the area served. Beyond that, they should be regarded as community and regional health facilities capable to varying degrees depending upon size and location of mounting research and training programs and of providing resources for tissue typing, organ transplantation, the management of problems in hemostasis, and for other clinical and diagnostic purposes. If the regional



blood centers are to perform these and other functions as an integral part of the health care system, the Panel strongly recommends that they be located in proximity to, and have close organic relations with, universities and major hospitals and medical centers.

It is unrealistic to project the evolution of regional blood centers without consideration of the available professional manpower essential for proper direction and leadership. There is an acute shortage of qualified medical directors even for existing community and regional blood centers, and this situation is progressively worsening. There are no established training programs anywhere in the country today capable of filling this urgent need. The Panel recommends as a matter of high priority that support be provided for the creation of appropriate facilities to attract young physicians and give them the training and experience necessary to become directors of the nation's regional blood centers. Without such training programs, the development of regional centers will be delayed and the quality of their services will suffer.

1.2.3 Pluralism

In keeping with the widely expressed feeling that commercialism be excluded from the nation's blood supply, the regional blood centers should be established as not-for-profit organizations. However, in developing the operational structure of the centers, it is important to encourage diversity so that the centers are not all cast in the same mold. Many, of course, will be associated with the American Red Cross, others will be free-standing institutions and some will be closely related to universities, hospitals or medical



societies. In all cases, it is important for the policy-making board of the regional center to have effective representation from the public-at-large, medical and hospital groups, and, where appropriate, from special consumer groups such as the hemophiliacs. The Panel is of the opinion that such pluralism is highly desirable both in the organization and the operation of the regional blood centers. It will stimulate recruitment of able and imaginative professional and managerial staffs, facilitate innovation and create healthy competition among regional centers.

1.2.4 Coordination at the National Level

Regional centers, even if capably directed and efficiently managed individually, do not by themselves constitute a national blood bank system. The present haphazard, often quarreling, uncoordinated "non-system" can no longer be tolerated. There must be close cooperation and effective coordination at the national level to assure that national needs and goals will progressively be met. There are several alternatives possible for forging a true national blood banking network.

One of the three existing national organizations (American Association of Blood Banks, American National Red Cross, and Council of Community Blood Centers) could be designated as the official chosen instrument, with the mandate to create an integrated national system. Unfortunately, none of the existing organizations clearly dominates the field as the natural choice. Selection of any one of the three would be bitterly resisted by the others and would inevitably result in wrangling and discord, with predictable deterioration of



services. A monolithic national structure would also reduce the advantages inherent in diversity.

An existing federal government agency, or a newly created one, could be empowered to weld a single national system out of the existing resources. This too is a less than optimal choice to be considered only if other alternatives fail. It would suffer from all the disadvantages cited in the paragraph above, plus being unnecessarily costly. The existing regional blood centers maintain their day-to-day operations without government subsidy and, with few exceptions, are financially sound. There is little doubt that the contemplated centers can also be self-sustaining after a short start-up period when moderate deficits may be incurred. There seems little need to create a new and expensive bureaucracy when we have acceptable alternatives that are less costly.

The three existing national blood bank organizations, which collectively account for more than 85 percent of the total blood supply, could be encouraged to form a coalition and create a new operating body. This central agency would serve as the focal point for a national network of existing and proposed regional units. It could serve as a central planning body, and undertake such broad programs in behalf of the constituent organizations as a national donor recruitment campaign, the development of uniform accounting procedures, specialized training and demonstration projects, and others.

The Panel is of the opinion that the third alternative--a coalition of the three major national blood bank organizations--is clearly the most desirable one at the present time. The three organizations should be encouraged to



compromise their differences and concentrate on the broad national health care goals to which they all subscribe.

1.2.5 Blood as a National Resource

The National Heart, Blood Vessel, Lung, and Blood Act of 1972 establishes quite explicitly the principle that blood is a national resource. The nation's blood supply, wherever collected, is the property of all the people, and represents a shared responsibility for a common supply.

Acceptance of this broad and humanitarian social doctrine inevitably evokes certain important practical conclusions. First, if there is a national "pool" of blood it exists for everyone, and access to it must be based solely upon medical need. The system as a whole becomes responsible for the lifelong requirements of those specially dependent upon blood and blood products, such as the hemophiliac or the child with chronic anemia, and for the acute and short-term requirements of the surgical patient or the victim of trauma, regardless of ability to pay. Second, the assessment of special fees contingent upon the replacement of blood used becomes unacceptable. It is a punitive device that adds only marginally, if at all, to the blood supply. Two of the three major blood organizations have already committed themselves to abolishing replacement (or "nonreplacement") fees. However, since some large blood banks and many hospitals are dependent upon such fees for a variable portion of their blood supply and for a significant part of their financing, careful planning will be necessary to determine how best to phase it out. Third, the unit credit system for blood now becomes an anachronism. It is a vast,



laborious, and expensive accounting system that would serve no useful purpose if all citizens had a basic right to share in the nation's blood resource, and all charges were assessed on the basis of cost. Fourth, there would no longer be a need to perform the complicated task of tracking individual credits from region to region across the country as people move about for whatever reasons of climate, medical care, or employment opportunities. Each region should accept responsibility for the blood needs of all its people anytime, whether they are long-time residents or transients who may be there briefly for highly specialized medical or surgical care. The country's blood supply needs to be so efficiently managed as to expedite rational and systematic movements of blood to balance inventories. Blood should travel freely from region to region (and perhaps even globally) according to broad needs and carefully planned inventory strategies, rather than merely to satisfy the credit requirements of isolated individuals.



Development of a comprehensive national blood program must consider the regulatory process as a key component if there is expectation of improved technology of transfusion and development of new products derived from human blood. In the past, regulatory agencies in the health area have operated largely as self-sufficient programs which have established standards of safety and efficacy internally and examined new procedures and products for licensing from this point of view. The effect of this posture has been to detach the regulatory agencies from the general scientific and clinical communities and to create an environment in which it was difficult to employ the best available opinion in formulating regulatory standards. By virtually total emphasis on safety of products and procedures, it has become difficult to weigh adequately the potential values of proposed advances in health care. Thus, the regulatory agencies have come to appear as largely passive, seemingly arbitrary barriers which new products and technologies must hurdle. A subtle but distinct atmosphere of adversary relationship with scientists, health care agencies and industry has emerged around the regulatory process in general. Regulatory processes which may be appropriate for the control of strictly industrial, economically motivated activities do not seem appropriate for the regulation of this field of activity where both the source and the beneficiary of the services are the American public

The need for effective regulation in the future is unquestionable. There is adequate evidence that legally required minimum standards, adequately enforced, are needed to protect the public. Hopefully, regulation will be carried out in



such a way that minimum required standards will not stifle the attainment of higher standards by the majority of operations, as may well now be the case. What seems clearly needed is to bring the regulatory agency into the national blood program as an active vigorous component, participating in and fostering appropriate and necessary developments in the field by engaging itself with the scientific, clinical and industrial communities in a positive way. In so doing, it must not relinquish its role as an objective evaluator of the cardinal problems of safety and efficacy. On the other hand, by better communications with the other functional components of the national blood program, it will be better appreciated by those who are primarily affected. A more harmonious process may be expected in which the flow of scientific research developments to the health care system will be greatly facilitated.

It is instructive to examine some of the realities which regulatory agencies must face in today's society. As part of the Executive Branch of Government, they sit uncomfortably close to the political process. Mistakes of judgment which may occur even after the best possible evaluation of scientific knowledge exposes them to attack possibly for only political advantage. This problem is particularly serious in this era when the public is being led to expect, quite unrealistically, "absolute safety" in all matters which are governmentally regulated. It is inevitable that errors of judgement will occur even when the process of prospective evaluation has been flawless and entirely well intended. This state of affairs makes delay in decision-making an attractive alternative to assumption of the risks inherent in making decisions. The historical difficulties which



have plagued regulatory agencies all too long can, in part, be understood on this basis.

How might this problem be overcome? We propose that a mechanism be established by which responsibility for decisions about standards of safety and efficacy be shared with independent groups of expert nongovernmental scientists and health care workers representing the public interest whose personal fate is not directly exposed to political attack. In this way the regulatory bodies would not solely bear the brunt of decisions which retrospectively turn out to be incorrect. A forum would be provided in which potential risks and uncertainties could be examined in relation to potential gains of improved and extended health care resources. Such a group would provide a mechanism to make available to the regulation process the best opinions that can be found within our society as a whole with regard to specific regulatory decisions. It would eliminate the need for the regulatory agency always to have within itself universal expertise capable of evaluating, at the highest level of competence, all possible problems which may come before it, an obviously impossible requirement given the limitations of budget and scientific manpower. Finally, it would accomplish another socially desirable goal by transferring a portion of the responsibility for decision-making directly to the public sector which is itself affected by the regulatory process.

It is also recommended that the Bureau of Biologics be encouraged to develop increased intramural research competence in the field of blood transfusion, blood products and related areas. This would provide the agency with immediately



available resources to deal with regulatory problems and provide an effective working interface with the related scientific and clinical community of the entire country.

Under such a program, the regulatory agency would still be solely responsible for enforcement and the general administration of the regulatory process. Failure in this respect should impact directly upon the agency. Public participation in the establishment of reasonable regulatory standards will in no way stand between the agency and the Executive Branch of Government or the Congress on such matters. Furthermore, the public groups assembled to aid in the development of standards should have no role, direct or indirect, in enforcement functions.

It is not the purpose of this discussion to present a detailed proposal for implementation of the program that has been suggested. This should be done by persons or agencies with legal and organizational expertise who have administrative responsibility in this area. It is possible that additional legislation will be required to implement this program effectively and this need should be considered. In broad outline, the program might function in the following way.

A Committee on The National Blood Program should be appointed by the Secretary of Health, Education and Welfare. It should be a standing committee and serve as a national policy-making body. Its membership should be based upon individual expertise and interest. It should have public, as well as professional and scientific representation, and appropriate liaison with the Bureau of Biologics of the Food and Drug Administration and other government agencies. This Committee would appoint a



group of standing subcommittees in the several areas of blood services, responsible for surveillance of specific areas of the National Blood Program with respect to scientific, technical and clinical developments. On request of the Bureau of Biologics or of the Committee on the National Blood Program, these subcommittees would be charged with the development of appropriate regulatory standards for new or revised procedures or products. Membership on the subcommittees would again be on the basis of individual expertise, and would not be representative of the several component agencies and organizations which comprise The National Blood Program. The subcommittees would be expected to develop the best scientific consensus available as the basis for their recommendations and to make use of ad hoc members, working groups, and appropriate consultations. Ad hoc subcommittees could be formed to deal with specific problems.

After confirmation by the Committee on The National Blood Program, the recommended standards would be transmitted to the Bureau of Biologics for review, acceptance, or comment and returned within a specified time period. If accepted, the recommendations would be published and administratively activated. Appeals from proposed or adopted standards would be directed to the Bureau of Biologics and if merit is found in such an appeal, the problem would be referred again to the appropriate subcommittee. The subcommittees could serve concurrently as a scientific resource of the Bureau of Biologics. The Bureau of Biologics would retain all powers to respond to urgent and emergency situations by issuing interim regulations for a defined period without consultation with the Committee on The National Blood Program.



The scope of the Bureau's responsibility should not be limited to the licensing of products but should extend to the whole range of materials and services involved in transfusion therapy. Thus, all materials, drugs, chemicals, apparatus, procedures, and services subsumed under The National Blood Program should be transferred to the Bureau of Biologics for regulatory control. The Bureau of Biologics would develop appropriate procedures for evaluating products, procedures and the proficiencies of blood transfusion services. In this way, uniform standards for a nationwide blood program can be established and enforced.



Creation of a national blood data center is vital to the development of a coordinated, effective and forward looking national blood program. Reliable statistical information on the American blood complex, even for such elementary facts as annual blood collection, usage, outdates, component production, and plasmapheresis, is almost nonexistent. The available data are chiefly episodic and incomplete, with the possible exception of the single year, 1971, when a national survey was conducted by Booz, Allen & Hamilton under contract with the National Blood Resource Branch of the National Heart and Lung Institute. Without the machinery for collecting quantitative information on a regular, reliable and comparable basis, it is virtually impossible to monitor the system, to manage it efficiently, or to plan properly. There is a clear and urgent need to establish a national blood data center either under the aegis of an existing federal agency or, if possible, as a joint though independent activity of the three national blood bank organizations. Close cooperation with the regulatory agency for blood would be highly desirable to ensure that essential vital statistics are made fully available by all blood agencies, and on a timely basis.

The National Blood Data Center would, in a methodical and ongoing fashion, collect statistical information essential to gauge the health and plan the future direction of the nation's blood resources. It should lay the groundwork for uniformly recording certain essential operating data. Eventually, it must also develop a uniform accounting system, so that costs and charges across the country may be compared, and the cost effectiveness of individual regions and the



system as a whole can be assessed. In addition, the Data Center should in due course serve as a laboratory for operations research and be able, for example, to examine critically the anomalies in the system, to assess the impact of population trends and social changes, and to predict the fluctuations in blood supply and demand attendant upon the introduction of new surgical procedures or new cancer therapies.

Approximately half of the country's blood resources derives from the pharmaceutical industry, with its ability to provide both bulk and selected plasmas by plasmapheresis. As private corporations in a highly competitive industry, pharmaceutical houses would naturally be reluctant to publish their proprietary operating figures. It is to their credit that representatives of the large plasma collectors and fractionators have indicated their willingness, with the proper safeguards for anonymity, to participate in a national data gathering effort and even to provide financial support for such an operation.

A National Blood Data Center can provide the information for regularly monitoring the health, growth, and adequacy of the system. A number of appropriate indices are readily apparent.

1.4.1 Supply

Publication on a regular basis of the figures for the total supply of blood, plasma, and their products would serve as a gauge of the growth and adequacy of the system. Inclusion of the percentage of the supply obtained from voluntary donors would mark the progress toward the goal of a totally volunteered supply.



1.4.2 The Use of Blood Components

The use of blood components not only stretches the available blood supply, but more importantly, constitutes better medical practice. The percentage of whole bloods that is separated into components, and more specifically, the proportionate use of packed cells versus whole blood for transfusion constitutes a simple test of the degree of sophistication of clinical transfusion therapy. There is little doubt that at least 50 percent of all blood transfusions should consist of packed red cells, and in the eyes of some, this figure should approach 100 percent.

1.4.3 Outdated Blood

The percentage of bloods outdated can, within certain limits, serve as a measure of the system's efficiency. A very low outdate figure (under 1 or 2 percent) in general means an inadequate supply and periods of serious shortage; a high outdate figure (in excess of 15 percent) is indicative of poor management. It should be clear that outdateding in the present context refers only to red cells, and that it is expected that as many as possible of the other constituents of the whole blood would be salvaged. The outdate figure serves as a rough chart of blood shortage or blood wastage, the Scylla and Charybdis that plague all blood bank managers. In the absence of more precise operations research data, it would seem that a figure between 4 and 8 percent would be reasonable and acceptable in the light of present technology.

1.4.4 Hemophilia

The quality, adequacy, and cost of the care of the hemophilic can serve as a critical barometer. In its way it measures the total supply of blood and fresh plasma, the use of components, the efficiency of the fractionation process, and the cost effectiveness of the entire system.

1.4.5 Hepatitis

The incidence of post-transfusion hepatitis, currently the most frequent serious complication of blood therapy, is an important public health indicator of the number of hepatitis carriers in the population and the effectiveness of hepatitis screening procedures. The type of data collection envisioned here is not the traditional retrospective reporting of cases, which is notoriously incomplete and of little value, but rather the deliberate and methodical search for cases as is done from hospital records by the Health Department of the State of New Jersey or, better still, by prospective surveillance programs in selected populations and the careful follow-up of blood recipients for long periods of time. The latter procedure, though expensive, can serve to monitor the blood supply not only for the hepatitis virus but also for the transmission of other disease agents, and can thus begin to utilize the donor population as an important epidemiological tool.



PART II

THE PROBLEMS AND PROPOSED PROGRAM



PART II
THE PROBLEMS AND PROPOSED PROGRAM

2.1 BLOOD RESOURCES

The charge to the Blood Resources Panel was divided into five general areas with a task group assigned to each, as follows:

- Blood Collection
- Fractionation and Preservation
- Laboratory Procedures and Controls
- Blood Utilization
- Systems Management.



There were, in addition, four subgroups in Transplantation, which will be considered separately. These subgroups directed their attention to (a) clinical immunological problems, (b) clinical non-immunological problems, (c) basic immunological problems, and (d) basic non-immunological problems.

2.1.1 Blood Collection

Four problem areas were identified by this task group: donor recruitment, collection equipment, donor selection and care, and personnel.

Donor Recruitment

Recruiting donors to provide a reliable and adequate supply of blood, plasma, and human organs is the keystone of a successful national program for blood transfusion and transplantation. Both blood and plasma have been chronically in short supply. There are recurrent, almost annual emergency appeals for blood in many communities during the summer and the Christmas-New Year holiday. Some 375,000 liters of plasma were imported in 1971 from underdeveloped countries for fractionation in the United States. The movement toward a totally voluntary blood supply complicates the recruitment problem, which will be further compounded manyfold if plasma is also to be obtained on a voluntary basis. Special problems are foreseen in the increasing number of clinical situations where a single donor is needed for a specific blood component (such as HL-A matched platelets or a specific antibody), and particularly in obtaining cadaveric organs for transplantation.



The few existing studies on the profile of donors of blood or organs, and why some people are motivated to give while so many others are reluctant, are superficial and only marginally useful. Experts in the fields of human motivation and social organization need to probe deeply into these matters. In addition, experts in communication must examine the roles of the various media in disseminating information and educating the public about blood and transplantation. Systems analysis of the merits and shortcomings of existing recruitment techniques would provide a stronger base for evolving more successful strategies.

The cumulative knowledge gained from these approaches will provide the framework for broad, non-competitive national donor recruitment. This would be an ongoing coast-to-coast campaign designed to reach those groups and individuals in the population most likely to donate blood or organs, and to educate the young and the reluctant about the importance of giving. The story has to be varied, as it appeals to several audiences; and it must stimulate the continuing response, born of understanding, which alone can guarantee an optimal supply to meet the growing and changing needs of medicine and surgery.

Collection Equipment

The use of blood components has greatly expanded the effectiveness of transfusion practice. There are, however, wide differences in the physiology of the various cellular and protein components of blood which result in strikingly different quantitative limits to donation of the respective elements. There are also comparably different requirements



for effective transfusion dosage. However, the optimal conditions for collection procedures and equipment are geared to the red blood cell. Effective use of the blood resource requires greater flexibility in the methods and equipment for collecting blood and its constituent parts. To provide this flexibility, a broad program of study is outlined to learn more about the physiology of the clinically useful components, their physicochemical properties, and the optimum conditions for collection and storage; and to develop improved materials and equipment for collection and processing.

A serious limiting factor to the processing of blood components, and parenthetically also to the use of frozen blood, is the need to maintain a "closed system," not to breach the integrity of the original collection container assembly because of the risk of bacterial contamination. A practical "docking" device that would permit repeated entry into the blood container without risk of infection would be enormously useful, and its development should be given high priority.

Donor Selection and Care

The rapidly increasing use of a single donor for plasma-pheresis or cytopheresis to obtain large amounts of selected plasma or blood components (e.g., a donor with a high-titered antibody or one having HL-A matched granulocytes for a specific patient) should focus attention again on the safety of the donor. We need to know more about the amounts that can be safely provided at one time, and what the long-term effects may be on the donor. The donor population's almost universal use of medications (analgesics, tranquilizers, contraceptive



pills, etc.) may have important implications for the clinical effectiveness of specific components (e.g., aspirin and platelets), and for the health of the recipient, and should be more systematically examined. Also, approximately two percent to five percent of blood donors experience some adverse reaction following donation. Though rarely serious, they are unpleasant and serve as a brake to repeated donations. More careful studies are needed to pinpoint the reasons for these reactions and to develop procedures for avoiding them. Donor registries on a regional or national scale have been advocated as means for detecting the individual capable of transmitting a serious disease such as hepatitis. The effectiveness and the cost of such registries need to be critically examined.

Personnel

Donor recruitment has hitherto been done largely by volunteers and well-meaning amateurs. If the blood supply is to be expanded, there will be need for a professionally trained full-time recruitment staff for obtaining blood and organs. The growing use of highly sophisticated equipment for cytopheresis also will require a cadre of specially trained people who are not now available.

Recommendations

1. Conduct systems analysis studies of the present donor recruitment system, the social and psychological factors that influence the non-donor and donor, and the organization of the donation process.
2. Study the biological and physiochemical aspects of blood component collection and preservation.



3. Develop new instrumentation for collecting blood and separating blood components.
4. Establish guidelines for the safety of the donor, and study the risk factors in plasmapheresis, cytopheresis, and hyperimmunization.
5. Develop professionally trained donor recruitment personnel.

2.1.2 Fractionation and Preservation

Centers of Excellence

The concept that human plasma can be fractionated and successfully preserved arose as a direct by-product of the needs of the Armed Forces in World War II. The desire for a therapeutically effective oncotic agent led to the isolation of human serum albumin in a form which could be easily packaged and transported without diluent or refrigeration. Essentially all of the other fractions of plasma arose as by-products of this work. These included therapeutically valuable substances such as gamma globulin, fibrinogen and antihemophilic factor. Improved methods for the separation and preservation of the cellular components of blood similarly arose in large part from the needs of the military, this time during the Korean conflict. All technological and scientific advances in the utilization of blood resources during the subsequent 20 years has drawn significantly on these assets. A majority of the key personnel who are engaged in fractionation, preservation, or the production of blood products obtained their original training and inspiration in comprehensive centers such as the one at Harvard under the late Edwin Cohn. Indeed, essentially no funding existed for blood preservation research during this interval except for



the modest support of the Department of Defense. Even the processing of frozen red cells, a potentially valuable new product for the civilian area, was developed in large part through military support. The rare new scientist who has initiated research on blood preservation or fractionation during the past two decades has entered the field almost by chance and often has obtained his training from unstructured programs in some other discipline. To rejuvenate this field and to recapture the philosophical and innovative spirit so necessary for future advancement, it is deemed a matter of high priority to reestablish a few centers of excellence, to pursue broad programs of basic research and development in protein chemistry and plasma fractionation, and to attract and train creative young people.

Metabolism of Red Cells and Preservation of Liquid Blood

A major facet of current blood transfusion therapy depends upon the ability to preserve red cells in vitro so that they survive and function when transfused into a recipient. In the United States, most of the eight to nine million units of blood intended for transfusion therapy annually are collected into a solution containing sodium citrate as an anti-coagulant, glucose as a red cell energy source, and citric acid to lower the pH [acid-citrate-dextrose (ACD) solution]. A less used, but more effective licensed solution is citrate-phosphate-dextrose (CPD). When blood is kept at 4°C for up to three weeks in either of these anticoagulant solutions more than 70 percent of the red cells retain their ability to circulate in a compatible recipient. (Arbitrarily, red cell preservation is considered adequate when 70 percent or more of the stored cells survive for 24 hours after transfusion.) Maintenance of such viability at 4°C is dependent



upon continued red cell glycolysis. The limitation in our knowledge regarding preservative solutions is underscored by the fact that, despite the temperature reduction, the storage period is short compared with the normal in vivo red cell life span of four months. Extending the useful shelf-life by even a few weeks would markedly increase the flexibility, improve the logistics of supply for civilian and military needs, and reduce the wastage due to outdating of a product often in critical demand.

Existing knowledge is available to permit a shelf-life with respect to viability of 28 to 42 days. Under most conditions of storage, the correlation is good between the level of intra-erythrocytic adenine nucleotides at the time of infusion and the subsequent post-transfusion survival of the cells. Accordingly, efforts have been directed at preventing the loss of adenine nucleotides on the one hand, or restoring them in long-stored cells on the other.

Until recently, most attempts to improve red cell preservation at 4°C have concentrated only on means to extend the post-transfusion survival percentage. It has been known for 16 years that the oxygen dissociation curve of the red cell shifts to the left during storage, which would appear to impair the ability of such cells to deliver oxygen to the tissues of the blood recipient. Only within the last four or five years has it been appreciated that this effect is due to depletion of red cell 2, 3-diphosphoglycerate (DPG). While stored cells retain the capacity to resynthesize DPG in vivo following transfusion, several hours to days may be required for significant DPG regeneration and restoration from the left-shifted curve to take place. This effect would appear



to be unimportant when only a single or a few units of blood or red cells are transfused into a recipient; however, it may become critical when massive transfusion therapy is required, as for severe trauma or complex surgery. In currently used liquid preservation of the optimal oxygen delivery function is maintained for only a few days. There is need for research dealing with red blood cells in a liquid state to improve supply, quality and clinical effectiveness by increasing shelf-life with respect to viability, oxygen transport function, and suitability for typing and crossmatching; and decreasing the concomitant infusion of potential or actual detrimental factors such as potassium, breakdown products of leukocytes, microaggregates, and others.

Frozen Blood

The feasibility of preserving red cells in the frozen state has been established for over 15 years. The clinical use of frozen red cells has been severely handicapped by lack of simple, inexpensive, disposable washing systems. At present, several companies are producing red cell washing systems that are available for study. A further limitation that prevents full exploitation of frozen blood is the requirement that the red cells must be used within 24 hours after thawing. A foolproof "docking" device to prevent bacterial contamination would be very helpful. Also, the possibility of rejuvenating outdated liquid-stored red cells prior to freezing needs to be more fully explored.



At present, the preservation time is one to three days. Optimal storage conditions remain a problem and patients often become refractory because of isoimmunization after multiple transfusion.

The desired objective is platelet storage without freezing for the longest possible time while retaining viability and hemostatic effectiveness, and without introducing toxic substances. There is need for:

- Basic studies of metabolic changes occurring in platelets during in vitro storage
- Development of new methods of collection (e.g., the use of prostaglandins) and new methods of storage to permit full retention of hemostatic effectiveness, with a seven-day or greater period being highly desirable
- Development of reliable in vitro predictors of in vivo hemostatic effectiveness
- Improved methods for matching platelets and/or preventing isosensitization.

Preservation of platelets by freezing has been achieved, but the preservatives in some cases are potentially toxic, the methods are cumbersome and expensive, and the hemostatic effectiveness remains to be established. A cost-effective means of platelet freezing would increase dramatically their availability in smaller hospitals and in large cancer services.

There is a developing need for large quantities of granulocytes to treat neutropenia induced by disease and therapy, a need which is likely to increase. While harvesting of

granulocytes is feasible, yields are poor, the in vivo life span is brief, the equipment is cumbersome and expensive, and their availability is limited. Preservation at present is feasible for freezing only relatively small quantities. Information regarding reconstitution is scanty with respect to both viability and function. Matching for histocompatibility antigens would appear to be important but is not generally available. Basic research into granulocyte biochemistry and physiology is badly needed, as is separation and storage technology. Research into the potential of in vitro granulocyte production using culture methods has been proposed. Finally, clinical effectiveness and dosage requirements need to be defined.

New Methods of Plasma Fractionation

The methods almost universally employed for production-scale plasma fractionation have been essentially unchanged for more than 25 years. There is urgent need to take advantage of new technology and to apply new methods of fractionation that are more efficient and less costly. For example, the procedures used to isolate and concentrate factor VIII result in loss of some 80 percent of the starting material. In addition, there are many proteins in plasma whose isolation in quantity will permit studies of their nature and significance in the cause and cure of disease.

Other areas for new product development include synthetic plasma volume expanders, synthetic hemostatic agents, and synthetic oxygen transport substances. The development of an inert, excretable, synthetic plasma volume expander without any untoward side effects or toxicity would be an



important contribution for the treatment of hemorrhagic and septic shock, common problems in civilian and military situations. Basic information is needed on the molecular biology of the plasma proteins involved in clotting that could lead to the development of synthetic hemostatic agents. Finally, there needs to be extension of the intriguing studies dealing with synthetic oxygen transport substances such as the fluorocarbons and microencapsulated hemoglobin.

Recommendations

1. Establish centers of excellence for basic research in blood cell physiology and protein chemistry; develop new chemical and engineering approaches to the separation of cellular components and fractionation of plasma proteins; and foster personnel training.
2. Promote studies on the red cells and other formed elements of the blood to extend their clinical usefulness and their preservation in the liquid and frozen state.
3. Develop new synthetic materials for the treatment of shock, the support of hemostasis and the transport of oxygen.

2.1.3 Laboratory Procedures and Controls

This Task Group dealt with the procedures to which a freshly collected unit of blood is subjected in order to classify it and make it ready for transfusion. The serological tests involved in classification have achieved a high degree of reliability and reproducibility, and the major source of serious error here is not technical but clerical. The Task Group recommended a feasibility study of a uniform registration and records system for blood banks, using standardized forms. There is precedent for this in the standard



forms used by otherwise competing commercial groups; i.e., credit cards, bank checks, airline tickets, etc. This would also simplify the collection of statistics on a regional and national basis.

Further studies are needed to develop automated devices which would be modular and suitable for antibody identification, crossmatching, and other repetitive procedures. The identification of special donors is now being done by a number of separate and loosely coordinated efforts. It is recommended that there be a feasibility study to consider one nationwide screening and registration program to include not only red cell phenotypes, but also platelet, leukocyte, and plasma protein phenotypes and individuals with particular antibodies. The major problem, however, in the safety of a unit of blood is recognizing agents of disease transmissible from the donor to the recipient, and here attention is currently focused on the hepatitis virus.

Hepatitis

Hepatitis is the most frequent serious complication encountered in transfusing blood or blood products. It is estimated that this disease occurs annually in 20,000 to 30,000 transfused patients and is fatal in some 3,000. Of those acutely infected, 1 percent to 5 percent become chronic carriers of the virus and may transmit additional infections in the community, and may themselves also develop chronic liver disease.

The severity of this complication is known to the public and has led to widespread concern, escalating in recent years as



more blood has been used, for example, in cardiac surgery. The many cases in which surgery has been successful, only to have the patient die later of post-transfusion hepatitis have spotlighted the problem and led to public indignation and lack of confidence in the blood banking system.

A major advance in our ability to prevent post-transfusion hepatitis has resulted from the recent discovery of an antigen--the hepatitis B antigen (HB Ag)--which appears to be a component of one of the viruses causing the disease. This antigen is detectable in some carriers of hepatitis virus type B and methods have been devised for screening blood donors to detect such carriers. All licensed blood banks now carry out such tests, but unfortunately they have not succeeded in eliminating post-transfusion hepatitis. The method now most widely used (counterelectrophoresis) detects only 25 percent of infectious bloods. On the basis of the limited data so far available, even the most sensitive of current methods (radioimmunoassay) does not appear to detect all of the bloods that transmit hepatitis. This failure may be due to inadequate sensitivity for detection of small amounts of HB Ag; to masking of antigen by circulating antibody; or to induction of hepatitis by viruses, such as hepatitis type A, which are not associated with this antigen. High priority should therefore be given to research designed to:

- Increase the speed and sensitivity of HB Ag detection methods
- Evaluate ~~the~~ role of other viruses in the production of post-transfusion hepatitis



- Devise means for detecting carriers of such viruses.

New procedures should be fully evaluated and field trials conducted before they are incorporated into routine blood bank operations.

The recognition of the carrier state has revealed hepatitis to be more than a complication of blood transfusion. With an estimated 500,000 to 1,000,000 carriers of hepatitis, it becomes a serious public health problem of national proportions. How the viral agent is maintained and transmitted in the population is largely unknown. Only a small percentage of carriers can be accounted for on the basis of blood transfusion or the use of shared needles, as among drug addicts. There is abundant evidence that HB Ag is transmitted by diverse routes, but the reservoirs and the avenues and vectors for transmission (droplets, sexual contact, mosquitoes, etc.) remain to be demonstrated.

In addition to the epidemiological problems raised by the hepatitis carrier state, there are serious social and medical problems to be faced. For example, what does one advise the innocent carrier who is a dentist, school teacher, barber, food handler? Are they hazardous to the public health in the performance of their occupations and should they be isolated--the modern day lepers and Typhoid Marys? The carrier state appears to last for many years, perhaps for life. Are there means for treating or aborting it? What are the risks to the carrier himself of developing chronic hepatitis, cirrhosis, hepatoma, and premature death? These and other questions require answers.



The identification of HB Ag has made it possible to produce gamma globulin preparations with known high concentrations of specific antibody to this antigen. These may prove effective in preventing or modifying type B hepatitis infections in certain high-risk populations such as accidentally exposed medical personnel, patients and staff of artificial kidney units, and perhaps patients receiving large numbers of transfusions. Controlled trials are now underway to evaluate these possibilities. If these studies prove the efficacy and safety of passive immunization, further research will be required to develop safe means for stimulating hepatitis B antibody formation in donors in order to provide sufficient quantities of source plasma for manufacturing this product.

Much basic work is needed toward developing a vaccine for type B hepatitis. The key difficulty in preparing such a vaccine is the lack of highly sensitive means for detecting infectious virus. It is thus difficult to evaluate the safety of any product except by experiments in human subjects. This difficulty also has impeded research on techniques for inactivation or removal of the virus from blood components. Both chimpanzees and Rhesus monkeys have been found to be susceptible to infection with hepatitis type B virus. Unfortunately, neither species develops a significant illness. Further research is needed to evaluate the sensitivity of these and other primate species in comparison to man and to develop cell culture methods for demonstrating infectious virus. The availability of a test animal or an in vitro test for the virus would greatly accelerate development of a vaccine for active immunization against type B hepatitis.



There is need to devise means for measuring the effectiveness of the various laboratory tests and other procedures introduced to reduce the incidence of hepatitis in recipients of blood and blood products. Case reports are inadequate, since in many of them hepatitis is subclinical and, therefore, unrecognized and even overt cases are only spot-tily reported. A new type of surveillance has to be developed--ongoing prospective examination of selected recipient populations to serve as indicators for changing incidence of post-transfusion hepatitis. This surveillance mechanism, if carefully planned, could also serve as a very useful means for evaluating other disease transmission risks associated with blood transfusion.

There have been vocal advocates of national blood donor registries specifically directed toward the detected hepatitis carrier or those implicated indirectly in transmitting the disease. These are expensive and very laborious procedures whose usefulness has yet to be demonstrated. Before there is a national stampede in this direction, it is recommended that there be limited and carefully controlled studies of the epidemiological effectiveness, as well as the cost effectiveness, of such registries.

Other Transmissible Diseases

Blood may transmit infectious agents other than the hepatitis virus. Cytomegalovirus (CMV) and Epstein-Barr (EB) virus are present in the blood of many donors. This virus does not normally produce clinical disease in most adults; however, it may produce fatal illness in newborn infants and in patients whose immune response has been suppressed,



such as transplant recipients. Rapid means for detection of CMV and EB in blood may therefore be needed.

Malaria can also be transmitted by transfusion, and with the convenience and rapidity of air travel from areas of the world where malaria is endemic, this a growing problem. Present regulations do not permit transfusing blood from persons who have been in areas of the world where malaria is endemic during the three years prior to donation. This approach, though reasonably effective, undoubtedly excludes many potential donors who are free of malaria. A rapid and specific serologic test for malaria would be a highly desirable screening procedure.

A circulating protein known as fetoglobulin has been reported to be associated frequently with carcinoma of the liver; and another, carcinoembryonic antigen, to be associated with tumors of the digestive tract. Since the role of these proteins is unknown, the significance of their presence in blood or blood products needs to be investigated.

In the large view, there is the theoretical possibility that blood transfusion may serve as the vehicle for transmission of "slow" viruses, agents associated with the cause of leukemia and other neoplastic diseases, and other infectious agents. The blood donor and recipient population can be viewed as a very large epidemiological laboratory from which much useful information can be gleaned if we are alert to the possibilities. A trained epidemiologist should be included as a full-time staff member of the larger regional blood centers, and epidemiological capability should be part of the product safety surveillance conducted by the regulatory agency.



Recommendations

1. High priority should be given to hepatitis, which is a national public health problem. Studies should be directed toward the development of more effective screening tests; the biology and epidemiology of the carrier state; the development of passive and active immunization; and the creation of a reliable monitoring system to evaluate changes in the incidence of the disease and its complications.
2. Blood transfusion services provide a hitherto unexploited epidemiologic base for the study of disease. It is recommended that extension of these activities be supported.

2.1.4 Blood Utilization

Optimal utilization of human blood resource for the treatment of patients represents the ultimate goal of the entire blood collection, processing and distribution network. Blood used inefficiently and inappropriately is both a medical and a management problem. One approach to achieving the goal of better utilization is through education of medical students, and physicians, especially anesthesiologists and surgeons, in the rational, judicious and effective use of blood and blood components. At least as important is the need for trained medical directors for hospital and regional blood banks. These educational programs should be paralleled by additional training opportunities for technical and administrative personnel.

Establishing uniform principles and standards for transfusion would materially improve blood use. Responsibility for the development and continuous revision of such standards could be shared by all the professional organizations involved in the delivery of transfusion services.



Establishing standards for laboratory performance by transfusion services is the joint responsibility of the Committee on the National Blood Program and the Bureau of Biologics. Responsibility for enforcing the standards and for proficiency testing lies within the purview of the Bureau of Biologics. A variety of proficiency testing mechanisms already exist; some of these might usefully be incorporated into the Bureau of Biologics surveillance and enforcement procedures.

The administration of whole blood and its components presents potential hazards due to their antigenic properties, ability to transmit infectious diseases, and the chance for human error to occur during collection, processing, storage, and administration. The true incidence of patient morbidity and mortality attributable to the annual transfusion of millions of units of whole blood and components is unknown, though estimates obtained from well monitored transfusion services indicate that they are sizeable. The methodology and technical feasibility for eliminating most of these hazards now exist. These skills must now be applied under carefully controlled conditions, thus achieving the twofold purpose of greater safety and efficacy with appropriate clinical documentation. The pressing need for effective and safe utilization of blood and blood products can be met in part by establishing clinical transfusion services in all major hospitals. Their functions should include pretransfusion evaluation of individual patient needs for blood and blood products; collection of patient samples for ABO-Rh typing, compatibility testing and other procedures; administration of blood products; and monitoring of the effects of transfusion both during and after blood use to identify complications and to ensure prompt attention for the prevention



and treatment of complications. Universal use of transfusion teams would serve to reduce human error and provide close rapport between the blood bank director and the patient's physician. Pilot programs are needed to establish guidelines and qualifications for medical and paramedical personnel and for evaluation of effectiveness and cost.

The hospital blood bank laboratory is the central point for improving the safety of transfusion services. Attention is directed to the areas discussed below.

Patient and Donor Identification

Mistaken identity in delivery of medical care is serious and can be lethal. Serious accidents are encountered most frequently in giving blood transfusions. Mistaken identity can be avoided only by the development of a fail-safe system of identification for the donor, the transfusion unit, and the patient.

Laboratory Procedures and Instrumentation

More sensitive procedures and instrumentation are needed for compatibility testing in vitro. This is one of the critical elements in assuring safe blood transfusion. There is a need to reevaluate the quality of the pilot samples used in testing, as there is evidence that their suitability for this purpose is sharply reduced during storage at 4°C. There is a growing need for better methods, as well as for instrumentation, to perform platelet compatibility tests and HL-A typing of leukocytes and platelets.



Retrieving Patient and Donor Data

Both regional blood centers and hospital blood banks need reliable and inexpensive means of quick access to donor or patient records to identify preexisting problems and to assist decision-making when time is at a premium.

Recommendations

1. Establish educational programs for the practicing physician and surgeon and for the specialist in blood banking.
2. Establish clinical transfusion services and transfusion teams.
3. Develop and continually update standard transfusion principles and practices and their enforcement by appropriate inspection and proficiency testing.
4. Develop fail-safe methods for patient and donor identification.
5. Improve critical laboratory tests such as the crossmatching and the antiglobulin test and the development of sensitive, reliable, and inexpensive instrumentation for testing and for data retrieval.
6. Establish indications for the clinical use of the various blood components and of blood of varying ages, and develop methods to measure their clinical effectiveness.

2.1.5 Systems Management

Systems management is a way of directing a complex group of enterprises through the planning, organization, coordination and control of its human and material resources toward the achievement of predetermined objectives. It is, therefore,



a force of considerable magnitude. However, in contrast to scientific progress, system management has not yet been mobilized in behalf of improving the blood service complex, except in relatively isolated instances. It should be applied broadly to all aspects of the management of the blood resources discussed in this report.

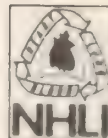
The earliest blood transfusions were carried out with the donor and the recipient lying side-by-side. Scientific and medical developments in the practice of transfusion therapy in the intervening years have made it possible for the donor to be separated from the recipient in both time and place-- in time by intervals of months and even years, and in place, by distances as great as our national boundaries. The "space" between the donor and the recipient is now occupied by a multitude of individuals and organizations performing a variety of simple and complex functions relating to the safe and effective transfer of blood and blood components from one human being to another. These individuals and organizations comprise what may be called the blood service complex. This picture of the blood service complex is helpful because it shows the exciting and almost limitless possibilities of providing blood service in a country such as the United States.

The blood service complex of the United States reflects these relationships and origins to a remarkable degree. The number of operating entities involved in the chain of events connecting donors and recipients is large; while the exact number is not known, it probably exceeds 5,000. Furthermore, while there is a reasonable discrete set of actions which occur in getting the blood from the donor to the recipient, i.e., processing, testing, distribution and the like, very



few of the operating entities--blood banks, blood centers, transfusion services, or whatever--actually are able to carry out the entire set. Instead, there are institutions which collect blood from donors, others which specialize in transfusing blood, and still others which collect blood and perform part or all of the intermediary activities, or less frequently, some of the intermediary functions and the transfusion services.

The thousands of operating entities which comprise the blood service complex have widely differing organizational forms; that is, they tend to be independently constituted. Their corporate structures may vary; and, if they are a part of some larger institution such as a hospital, the relationship to the hospital varies considerably from place to place. This means that they also tend to act independently. Local decisions are customary, even in such matters as pricing for services or choosing which services to offer, and determining donor recruitment strategies. Inducements to donors and commitments to recipients usually originate locally and are often without apparent pattern, a fact which works to the consternation of the public. This is especially true if more than one functional unit within the same community is bombarding the public with differing appeals to become blood donors. And in areas where a single regional blood center collects and processes the blood centrally, the patient may be variously billed for a transfusion, depending upon which hospital he used. Even in the American Red Cross Blood Program, which consists of 59 centers, the degree of operational independence of the individual centers is large.



The systems management process is now urgently needed by the blood service complex of the United States. The nation's blood problems can no longer be resolved by multiple, unique local solutions which are costly, inefficient, and often incompatible. Scientific progress is now being accelerated at a pace which affects all aspects of the field. There are new discoveries in cell separation and preservation. Processing is becoming increasingly individualized and differentiated to meet the needs of specific patients. More sophisticated and more expensive laboratory testing procedures are being introduced. Rapid developments in the virology of blood-borne hepatitis suggest that exciting breakthroughs will be possible within a relatively short time. But as scientific strides are made, the lag between discovery and application at the bedside will widen unless the resources and activities required for providing blood services are more efficiently planned, organized and controlled. The lack of sound systems management is already seriously slowing down the application of knowledge, in no small part because it is so costly to apply new knowledge under the present fragmented arrangement of service units.

Systems management begins by setting objectives. The lack of clearly stated sound national objectives concerning the blood resource has become a serious matter. National objectives are needed because health care has become a national problem and because blood has come to be regarded as a national resource. The Congress, for several years, has shown its strong interest and concern about the national blood supply by supporting research and development in blood and has recently affirmed its interest by calling for improved management of the national blood resource. National concern



about blood is further manifested by the recent actions of the Food and Drug Administration extending federal control to all blood banks, the considerable attention both in Congress and in all news media about the purity and safety of blood, and the emphasis upon the importance of an all-voluntary blood supply by the leading blood bank organization.

To achieve national and local objectives, new organizational forms will have to be developed. Thus the concept of shared common facilities in certain functions will require new coordinating mechanisms. Establishing networks of small blood units for better blood economy or improved and more efficient laboratory testing are other examples. As the idea of regionalism spreads and as the country moves toward "Total Responsibility Blood Regions," a mechanism for effective national coordination will have to evolve. Its function would perforce go beyond coordination of existing local and regional units. This mechanism must, for the health and effectiveness of the entire system be prepared to establish and review national goals, provide broad planning capabilities, and undertake surveillance of the system's performance from the medical and management points of view.

New manpower requirements can also be anticipated. Not only will new management activities require this, but it is also an unfortunate fact that the blood banking field is currently in urgent need of manpower training programs at every level, as is especially evident in the areas of clinical and scientific direction of blood bank units.



Management Information Systems

Since management is fundamentally a process of choosing between alternatives, the manager must have as much information as possible when a decision is reached, whether it is a matter of long-range planning, of capital investment, of developing a new product, or of scheduling a daily set of activities. Good information of the kinds required in management of the blood complex is unfortunately lacking. Of special value would be uniformly reported data from blood banks across the country to facilitate communication, coordination, and comparison and evaluation of blood services. Furthermore, capabilities are totally lacking for operations research, i.e., for developing needed specific information about the enterprise. For this reason, the development of a National Blood Data Center is regarded by the Task Group as a matter of high priority.

Measurement and Evaluation

The health care system in the United States is under intense scrutiny. Considerable emphasis is being placed, with some success, on developing methods for evaluating productivity and applying economic cost-benefit measures. The blood service complex is vulnerable to attack because there are no available data on performance and there are public perceptions of a highly arbitrary and heterogeneous economic structure.

One of the strongest arguments favoring the introduction of systems management to blood service is that it will result in improved service, in more economic utilization of the blood resources, and most important, in improved effectiveness



and efficiency. For these reasons, it is recommended that emphasis be placed on developing measures of activity and relating these to the objectives established for the program. Only in this way will it be possible to obtain secure and credible evaluation of the changes to be made.

Recommendations

1. Introduce the concepts of systems management to the development of regional and national mechanisms for the establishment of goals, planning, coordination and overall surveillance of performance.
2. Establish a National Blood Data Center to serve as a management information system and for operations research.
3. Introduce new training programs for professional and management personnel.



2.2

TRANSPLANTATION

2.2.1

Introduction

Living tissues and organs have been used to replace more than 2,000 kidneys, 200 bone marrows, and 150 hearts. Transplantation has become the accepted therapy for dealing with many of the 10,000 cases of end-stage renal disease which occur each year in the United States. This will surely extend to other tissues and organs as the underlying genetic and immunologic problems are solved. Since the solution of these problems is basic to the future of successful transplantation, a major effort in this direction is of the highest priority. Simultaneously, an effective regional and national program must be developed to take full advantage of the knowledge already gained and to translate with minimum delay new findings, as they come from the research laboratories, into useful clinical procedures. A train of new clinical problems will follow inevitably. Equally important are the social, moral, and legal problems involved in educating the public about transplantation and the logistics of procuring, distributing and preserving the donated organs. For the sake of convenience, the contributions of the subgroups in transplantation will be summarized under three general headings: the basic problems, the clinical problems, and the social and logistical problems.

2.2.2 The Basic Problems

Immunogenetics

Two genetic systems, the ABO blood group system and the HL-A system, are believed to define strong transplantation antigens in human beings. The ABO blood group antigens have been responsible for acute rejection of kidney and white graft rejection of skin, although they seem to be less critical in bone marrow grafting. The HL-A alloantigens are highly polymorphic and evidence is accumulating that the HL-A system is part of a chromosomal complex which also controls other immunological factors such as mixed lymphocyte reactivity and immune responsiveness.

Renal grafts between HL-A identical siblings do exceedingly well in recipients maintained on low immunosuppression, and bone marrow grafts from HL-A identical sibling donors have been successful in several instances, much more so than those from unrelated HL-A identical donors. Although several groups of investigators have presented evidence that HL-A matching of unrelated donors results in a statistically significant prolongation of kidney graft survival, HL-A matching of unrelated donors has not been as fruitful as matching of related individuals. With respect to renal grafts, it should also be stressed that many well HL-A matched grafts from unrelated donors do poorly, while many poorly matched kidneys do well.

In general, lymphocytes from HL-A identical siblings do not give in vitro mixed lymphocyte culture (MLC) reactions whereas those from HL-A identical unrelated individuals usually



do react in MLC tests. This in vitro response is correlated with the prognosis for graft survival; grafts from HL-A identical siblings are well accepted while grafts from HL-A identical unrelated donors are not as well tolerated. The question then arises whether there is a direct relationship between MLC reactions and graft acceptance or rejection.

HL-A identical siblings obviously share more non-HL-A transplantation antigens than unrelated HL-A identical individuals. How important are the non-HL-A differences? For renal grafts they do not seem to be as important a determinant for graft acceptance as they are in bone marrow transplantation.

Evidence is needed to establish whether HL-A antigens are indeed transplantation antigens in the strictest sense and, if they are, the relative importance of these antigens must be assessed. Perhaps HL-A is only a genetic marker closely linked to the real locus (or loci) determining the transplantation antigens. It also is possible that we are not yet able to match unrelated individuals with respect to all of their HL-A antigenic specifications, and it is because of this fact that unrelated but HL-A matched (according to present procedures) grafts do not do as well as grafts from HL-A matched related donors. This possibility deserves further study. Serological procedures currently used for typing (especially lymphocytotoxicity) apparently detect HL-A specificities only when they are present in sufficient density on the lymphocyte surface. Consequently, other serological procedures, either known or still to be developed (based, for example, on the antiglobulin reaction) should be investigated. Further studies on antigenic density of cell surface allo-antigens in various cells and tissues should be undertaken.



Nature of Immune Response and Immunologic Injury

The immune response to transplantation antigens is both cellular and humoral. Solid tissue grafts appear to be primarily, if not exclusively, destroyed by a cellular mechanism, whereas dispersed grafts, such as bone marrow, seem to be destroyed primarily by humoral antibodies. In recent years, however, evidence has been presented that solid tissue grafts, e.g., kidney grafts, may also be destroyed by humoral antibodies. This occurs in a dramatic way as a hyperacute rejection in those cases where the recipient has preformed transplantation antibodies. Evidence is emerging that slow deterioration of a renal graft, as expressed by vascular damage, may also be mediated by humoral antibody against transplantation antigens which either act directly or, more likely, indirectly by deposition of antigen-antibody complexes. With improving management of patients on immunosuppressive therapy, the antibody-mediated injury becomes more of a problem. The type of graft may play a role in the nature of the primary immune response. For example, a graft which is immediately vascularized seems to do better than a graft in which vascularization occurs by healing-in.

The graft-versus-host reaction is exemplified in a bone marrow graft where immunologically competent cells of donor origin react against the host. At present, HL-A matching, even with siblings, will not insure against this reaction.

It is becoming more and more apparent that stimulation by agents other than grafted cells may play a contributory role in graft rejection. This includes presensitization to transplantation antigens as a result of pregnancy and blood



transfusion and by cross-reacting microbial antigens. It has been observed that intercurrent infections may contribute to graft rejection. Infection may also act as an adjuvant by augmenting the response of auxiliary cells such as macrophages. The immune responsiveness of the individual to various antigens, including those responsible for eliciting transplantation immunity, has been shown to be under genetic control. Therefore, it can be predicted that poor responders to particular antigens may be better graft recipients.

The possibility that passenger lymphocytes in the graft may act as important immunogens needs exploration. The routes of sensitization, whether central or peripheral, i.e., whether sensitization occurs by presentation of graft antigen to the lymphoid centers or whether lymphoid cells are sensitized directly in the graft, are of both theoretical and practical interest. The whole area of presensitization (for example, by prior blood transfusions) needs reexamination in terms of the conditions under which it may either accelerate or retard graft rejection. With the demonstration that humoral antibodies can be responsible for hyperacute rejection of renal grafts, crossmatching became mandatory. At present, the routine procedure for crossmatching is lymphocytotoxicity. There is increasing evidence that this method is inadequate, since acute rejection has occurred in the presence of a negative crossmatch, while in several cases, there was no hyperacute rejection despite a positive crossmatch. New techniques for crossmatching which would allow one to distinguish harmful cytotoxic antibodies from beneficial, enhancing antibodies need development.



Continuous, qualitative assaying of the cellular and humoral responses during graft acceptance or rejection is needed. Cellular immune reactions can be assessed by mixed lymphocyte cytotoxicity, inhibition of macrophage migration, and other procedures. The humoral response can be measured by a variety of procedures. New and better methods for both of these immunological responses need to be developed.

Vascular lesions in renal grafts may occur several months, or even years, after grafting. Well documented morphological data suggest an immune mechanism as the responsible agent. The following explanations of this immunological reaction have been advanced:

- Recurrence of the original lesion
- A de novo immune reaction to a kidney-specific antigen rather than to a "transplantation" antigen
- Deposition of immune complexes formed from transplantation antigens and antibody.

Present evidence points to the third of these possibilities as being more important than the first two; however, the pathogenetic mechanisms underlying these lesions need further clarification.

Genetic control of the magnitude of the immune response to transplantation antigens and linkage of immune response genes to the major histocompatibility antigen system have been demonstrated in animal models. Genetic control and mechanism of action of immune response genes to transplantation antigens must be investigated in man.



Prevention of Rejection

Very powerful immunosuppressants have been developed in animals and some have been used successfully in the human graft recipient. Azathioprine, corticosteroids, cyclophosphamide, and antilymphocyte serum (ALS) have been used in various combinations. These drugs are directed primarily against the cellular response. Since their action is indiscriminate, the patient is immunologically deficient with susceptibility to infection and neoplasia. The drugs also have other undesirable side effects. Immunosuppressants of humoral responses (for example, for use with bone marrow grafts) and regimens of combined treatments with fewer side effects are urgently needed.

The preceding narrative has emphasized the necessity for procedures which will selectively suppress the host's allograft response. Two phenomena defined from animal models are possible candidates; namely, acquired immunological tolerance and immunological enhancement.

Tolerance has been defined as a specific "central" inability of an animal to respond to an antigen with which it had been confronted previously under certain experimental conditions. Immunological enhancement has been defined as the permanent survival or delayed rejection of an allograft as a consequence of the presence of specific allograft antibody in the recipient. In initial studies, enhancement seemed to be mediated peripherally, i.e., at the level of the graft, whereas tolerance operated centrally. Recent data raise questions about this dichotomy and the validity of the distinction between the two phenomena. Early demonstrations of

tolerance were in inbred animals treated in utero or as neonates with adult lymphoid cells from the donor strain destined to furnish the allograft. Later, tolerance was also achieved in the adult animal, but this required massive doses of cells. In contrast, enhancement has always been elicited in adults, and early animal models dealt with tumor allografts. Pertinent to human grafting is the recent evidence of successful enhancement of kidney and heart allografts in animals, particularly in the rat.

Tolerance induction in adult humans, in the context of the animal model, would require prohibitive amounts of allogenic tissues. The possibility of solubilizing presumed transplantation antigens and assessing their tolerogenic potential should be explored.

Since present clinical evidence indicates that enhancement may contribute to the success of kidney grafts, this approach to organ and tissue grafting deserves extensive exploration using the existing rat and mouse enhancement models.

In addition to the rat and mouse models, conditions for enhancement should be explored in other species. In the pig, the permanent survival of liver allografts and the ability of such grafts to promote the survival of other organ grafts of similar genotype is a promising research model. Information from such animal models should indicate the road for clinical investigations.



Graft Adaptation and Modification

Antigenic simplification of grafts after residence in allogenic hosts has been convincingly demonstrated for tumors in the animal model. Similar alterations in normal grafts should be explored as an interesting possibility. Evidence has been presented that cells and tissues maintained in artificial culture media in vitro before transplantation were accepted by allogenic hosts. The possibility of modifying organ and tissue allografts by this procedure should be further explored. Such modification might even be able to eliminate the graft-versus-host reaction in bone marrow grafts. The possibility of selective elimination of some immunocompetent cells from bone marrow should be explored as a potential method of obviating the graft-versus-host reaction.

2.2.3 The Clinical Problems

Successful transplantation of living cells whether they be heart, lung, liver, kidney, skin or bone marrow is dependent upon the same underlying biological requirements. The importance of achieving compatibility and immune suppression applies generally to all cells, although there are differences in the clinical problems posed by the functional failure of each type of tissue, and these problems are nearer solution for some organs and tissues than for others. For example, the success of heart and lung transplants in the long run will depend heavily upon the availability of appropriate external life support systems to provide the kind of flexibility in managing individual patients which is now possible in the case of the kidney. However, since most of

the clinical immunological problems are general ones, they will be considered together for all tissues in the present analysis.

Compatibility Between Patient and Donor

There are a number of problems to be resolved in this critical area, and the following are proposed as directions for research.

- Development of monospecific serological typing reagents
- Family studies of histocompatibility immunogenetics
- New methods of detecting histocompatibility markers
- Determination of the relative immunogenicity of various HL-A specificities
- Continuing evaluation of the predictive value of tissue typing tests for subsequent transplant survival.

Preimmunization

The patient's history of exposure to transplantation antigens is important to the outcome of a graft. Transfusions definitely induce immunization to HL-A antigens as well as to minor antigens. Almost surely, multiple transfusions will immunize against nonidentical HL-A donors. Hyperacute rejection and second-set phenomena are usually associated with the presence of ABO antibodies or preformed cytotoxic antibodies against antigens detectable on cells of the graft. Methods are available to detect some of these antibodies by crossmatching and they can be made more sensitive in certain



ways, such as adding antiglobulin or treating lymphocytes with enzymes. Nevertheless, we must develop still more sensitive methods for identifying those individuals who are presensitized. The following problems need examination:

- Role of non-HL-A antibodies in crossmatching
- Crossmatch tests for cell-mediated response
- Importance of plasma factors which block in vitro cell transformation
- Methods for avoiding presensitization as by blood transfusion
- Importance of previous exposure to bacterial antigens
- Circumvention of preexisting sensitization.

Immune Responsiveness

There is now considerable evidence that the vigor of the immune response to a specific antigen varies from one individual to another, and that in animals at least it is subject to genetic control. Further work in this area is warranted to learn more about the control of immune responsiveness in man, and to develop in vitro or in vivo tests for measuring the degree of immune responsiveness and its possible application to transplant survival.

Immune Suppression

The availability of chemical and biological immunosuppressive agents has been essential to successful organ and tissue transplantation. They have, however, posed many serious problems in that they are nonspecific and depress important



body defense mechanisms. It is extremely difficult to quantify their effectiveness or to standardize some of them; hence, suppressive drug dosage becomes a problem. The following are proposed directions for research:

- Development of improved methods of nonspecific immunosuppression
- Tests of the vigor of the rejection response
- Specific alterations of immune responsiveness.

Graft-Versus-Host (GVH) Reactions

These constitute a serious complication of bone marrow transplants, and attempts to circumvent them by immunosuppression with cytotoxic chemicals or antilymphocyte serum have achieved only indifferent success. Other methods have been tried, e.g., removal of lymphocytes by differential centrifugation or by thymidine suicide, and more recently, enhancing sera have been employed with only limited success. Further studies in this area are clearly indicated.

Supportive Care

Transplant recipient is immunodeficient and therefore susceptible to many viral, fungal, and parasitic infections, and may also constitute a hazard to the community. The epidemics of type B hepatitis associated with renal dialysis and transplant centers are rather alarming examples of the latter. Infections with agents such as cytomegalovirus, which are relatively innocuous in most individuals, can be serious and life-threatening in the transplant patient.



Patients undergoing marrow transplants are almost invariably deficient in platelets, granulocytes and erythrocytes, at least initially. Replacement of erythrocytes does not present a problem. Platelet support is available to some degree in most centers but much more can be done, especially with respect to supply and storage. Granulocyte infusion is possible in only a few selected centers. Thus, there are clear needs for more widespread availability of granulocyte and platelet transfusions. The relationship of HL-A typing to the survival and function of platelets and granulocytes needs further definition. The question of whether granulocyte transfusions are effective and under what circumstances, and the evaluation of their side effects when collected by various methods, remain as areas to be investigated.

In addition to the problems of cell component therapy, continued evaluation of isolation procedures is needed. At present, there is no hard evidence that laminar flow rooms, sterile food, and oral antibiotics really make a great deal of difference.

Late Problems

About 30 percent of patients at 100 days past marrow transplantation develop a severe diffuse interstitial pneumonitis due to cytomegalovirus, fungus or Pneumocystis carinii, or other etiologic agents. Clarification of these defects employing in vitro tests of cell-mediated and humoral immunity is needed. More empirical treatments, such as thymosin administration or thymus grafting, etc., should be evaluated in animal models.



Among the distressing late occurrences in transplant patients is the apparent reappearance of the patient's original disease, glomerulonephritis in the case of the renal transplant recipient or leukemia in a bone marrow recipient. In addition, as many as 5 percent of patients undergoing prolonged immunosuppression have been found to have primary neoplasms. Continued careful observation of long-term transplant survivors is clearly indicated, with special attention to unforeseen physiological and emotional sequelae.

Clinical Transplant Centers

The Regional Medical Program has taken the initiative and fostered the development of regional systems for treatment of end-stage renal disease. These, however, are of necessity service-oriented and designed to apply knowledge as it currently exists in the treatment of large numbers of patients. There is no emphasis and very little financial support for clinical or basic research designed to improve the results of transplantation. There should be support for research-oriented clinical centers for the following reasons:

- The results of cadaver renal transplantation have stabilized at a less than satisfactory level (40 percent or more fail).
- The results of other organ grafts, i.e., heart, liver and bone marrow are far less predictable and need even more extensive study before they can be considered therapeutic on a broader scale.
- Surgical technologies, typing and immunosuppression have not solved the problem of transplantation but only opened up a vast number of new areas for clinical and basic research.



- There are at present too few transplant surgeons, immunologists, internists, etc., with sufficiently broad backgrounds to advance knowledge in the transplant field. The establishment of major clinical transplant centers would provide a mechanism whereby such investigative collaboration could be stimulated and facilitated.

It is proposed that approximately 20 centers be established devoted primarily to clinical and basic research in transplantation of all organs and tissues. These should be competitively awarded and funded according to the peer review mechanism, based on the following areas of emphasis:

- Facilities and personnel for the optimal treatment of transplant recipients undergoing high-risk research procedures
- Facilities and personnel for the study, monitoring and manipulation of the immunological events resulting from or associated with transplantation
- An interdisciplinary approach to clinical and basic transplantation research
- The demonstrated ability to attract and train personnel for work in all aspects of transplantation research.

2.2.4 The Social and Logistical Problems

If the transplantation of organs and tissues is to realize its full therapeutic potential, a network of regional centers, coordinated at the national level, should be developed, to be responsible for public education, donor recruitment, organ retrieval, storage and distribution, and the centralized performance of laboratory tests and record-keeping. This integrated system is in many ways similar to that outlined

for the nation's blood resources, and there is every reason to expect that in many cases the regional blood centers will also function as the regional transplant resources.

Public Education

There is need for carefully planned programs to educate the public and the medical profession on the importance of transplantation and the need for organ donation. The voluntary health agencies can play a prominent role in such campaigns. Public forums are needed to discuss the ethical and social questions that are inherent in human transplantation, and there should be formal conferences between members of the legal and medical professions and legislators to define the legal issues and to promote legislation.

Brain Death

When dealing with cadaver organs, the problem of brain death, as opposed to cardiorespiratory death, becomes an important factor. It is well recognized that organs obtained from individuals following brain death have a distinctly better chance of survival than those removed from individuals who died a cardiorespiratory death. In addition, transplantation of the heart and other single organs requires that the circulation be maintained until the organ is removed. This can only be accomplished in those donors who have suffered severe brain damage and are thereby declared dead. The medical and legal professions have dealt with the problem and have devised a definition of neurological death (brain death) which is a suitable basis for collecting organs. However, to date only a few states have implemented legislation describing brain



death, and many other states have antiquated or inadequate laws which define death in terms of heart stoppage or other cardiorespiratory failure. If transplantation is to be extended to the national level, new legislation will be necessary. Past experience has shown that cooperation between the medical community and the legal community can stimulate the passage of laws, such as the Uniform Donor Gift Act which provides a basis through which individuals can donate organs for transplantation either during life or after death. Legislation should be extended to include the definition of brain death so that this most suitable category of cadaver donors can be made available to transplantation centers in all states.

Organ Procurement

It is strongly recommended that programs for organ procurement and other transplantation resources be established on a regional basis. This will be more efficient and more effective because trained personnel, appropriate records, and the essential legal and medical information will be concentrated in one place. Currently, physicians associated with transplant teams are expected to set up local programs and encourage cooperation among regional hospitals to participate as sources of tissues and organs for transplantation. At times these programs are competitive. For example, a heart transplant center may compete with a kidney transplant center for organs in the same community. When transplants of different organs or tissues are performed within a single hospital, there usually is a good basis for cooperative collection of organs and tissues; however, competitive tissue procurement occurs even now and will become increasingly important in the



future as transplantation is extended to include a greater number of tissues and organs. If we are to obtain the maximum benefit to be derived from tissue donation by an individual donor, it will be necessary to establish a cooperative regional system for the collection of tissues from each potential donor. This will facilitate the training of specialized personnel to perform the various tissue procurement procedures and assure compliance with the legal as well as the scientific requirements.

The education of physician assistants in the area of tissue procurement would seem the logical next step. Just as highly trained technicians can perform the majority of procedures necessary for blood banking and blood component therapy, a technician specially trained in tissue procurement should be capable of collecting cadaver organs and tissues for transplantation, thereby releasing highly skilled surgical and medical manpower for more suitable professional activities. It should be emphasized that such transplant technicians must function under close professional supervision.

Organ Preservation

Regional procurement, to be maximally effective, will ultimately require techniques and facilities for organ preservation. The ability to store organs for days, months, or perhaps indefinitely would enormously increase the available supply and make it possible to transport organs great distances.

Research in organ and tissue preservation can be divided into three categories: Cryogenic Storage, Hypothermic Storage, and Organ Cultures.



Cryogenic Storage

Cryogenic storage in most respects would be the ideal form and it may be the most difficult to attain. Its practicality has already been well established by successful storage of sperm, lymphoid cells and hemopoetic cells. Innovations must be developed for applying the experience gained in freezing of dissociated cells to tissues and entire organs. Cryogenic storage of organs is a long-term project; it will be expensive to develop and maintain, but once established, would provide the ultimate in versatility.

Hypothermic Storage

Hypothermic storage of cells for periods less than a week and most organs for less than a day is now in common practice. These methods are most likely to yield immediate useful results. Continuous hypothermic perfusion has been extensively utilized in storing human kidneys. Refining and simplifying these methods will aid in the transport of kidneys and in extensions of the technology to other organs. Just as ACD solution permitted blood storage for three weeks and revolutionized blood banking, so the development of simple hypothermic solutions would make the preservation of organs a routine matter. A storage period similar to that for blood would solve 95 percent of the needs in transplantation. High priority should be given to developing such simplified procedures.

Organ Cultures

Organ culture is an alternative method of preservation which may hold promise for certain specialized reasons. Lymphocytes



within an organ such as the heart could be differentially removed during the culture process. There is evidence that grafts devoid of lymphoid cells survive with less rejection. Some suggestive experimental evidence that cells can be altered by tissue culturing is also available. Though expensive, this means of preservation has the greatest potential in permitting some alteration of the organ outside the body. The natural media and numerous culture conditions could be altered to achieve the optimal alterations desired.

Organ Distribution

Every effort should be made to prevent marketing of human organs. Regarding all human organs as a priceless national human resource is the essential principle of organ distribution. A plan for national distribution should be organized from the outset, to make organs and tissues widely available. Their geographic origins are likely to be quite different from the sites of their ultimate use. A composite registry of all available organs maintained by a regional and national computer network is essential.



PART III

SUMMARY OF PANEL RECOMMENDATIONS

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3.1 BLOOD RESOURCES

1. Encourage regionalization by the development of regional blood centers and the creation of a national blood network coordinated and monitored by an appropriate national agency. The latter is a vital integrating function which can and should be performed by a consortium of the three national blood bank organizations--The American Association of Blood Banks, The American National Red Cross, and the Council of Community Blood Centers
2. Organize a vigorous year-round national recruitment campaign for voluntary blood donors. Initially this will, of necessity, make use of existing knowledge and resources for public education and information. Social and psychological studies of donor motivation and organization are necessary to achieve an ample supply of blood, plasma, and essential derivatives and byproducts



3. Make a concerted attack on hepatitis as a serious public health problem and include the development and use of more sensitive practical tests for detecting the carrier state, studies of the biology and epidemiology of the carrier state, and a coordinated program to develop passive immunization and active vaccination for this disease
4. Expand the scientific base by creating scientific centers of excellence for research and development in regional blood centers closely associated with universities or major medical installations
5. Establish training programs which are urgently needed to develop the highly specialized medical manpower, without which regionalization will be delayed and the quality of transfusion services to patients will suffer. (There is at present, an acute and growing shortage of qualified physicians to staff the nation's hospital blood banks and regional blood centers.)
6. Regenerate the plasma fractionation field by establishing in selected centers, research capabilities in protein chemistry and plasma separation: to develop new methods, particularly more efficient methods for purifying factor VIII; to isolate new plasma proteins that may have clinical or laboratory usefulness; and to train the requisite scientific and engineering manpower
7. Create a National Blood Data Center
8. Restructure the relationship between the regulatory agency and the blood resource.



1. Expand support for fundamental research in immunology, immunogenetics and other aspects of transplantation biology
2. Develop regional and national programs for organ procurement
3. Encourage public dialogue on the ethical and legal problems associated with organ transplantation
4. Develop improved procedures for organ preservation and storage
5. Improve management of the posttransplant patient, such as prevention of graft-versus-host reaction, better immunosuppression, prevention and treatment of infection
6. Establish transplantation research centers to stimulate interdisciplinary approaches to clinical and basic transplantation problems and to train personnel.



PART IV

THE LEGISLATION AND THE PROPOSED PROGRAM



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Section 413 of the National Heart, Blood Vessel, Lung and Blood Act of 1972 delineates 10 specific program requirements. These 10 legislative requirements are presented in Appendix B. Of the 10 requirements, number 6 by definition applies to all the projects as defined by the respective Blood Resources Task Groups. The other requirements, which refer to such items as epidemiology and etiology, bioengineering, etc., apply to varying degrees to the blood resource problems and to the field of transplantation.

Table B-1 of Appendix B represents the distribution of project areas with respect to the legislative requirements for the Blood Resources Task Groups. As may be noted from this table, the predominant transplantation emphasis is in the areas of Requirements No. 1 and 2, which refer to the epidemiology, etiology, and biological processes. Additional figures graphically depicting the relationship of the project



areas to the legislative requirements for each of the Task Groups, as well as a composite figure for all of the Task Groups, are included in Appendix B.



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National Hemophilia Foundation	Dr. Louis Aledort
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Pharmaceutical Manufacturers Association	Dr. Frank B. Voris
Stanford University School of Medicine	Dr. J. Garrott Allen
The Dow Chemical Company	Dr. Steven J. Cieciora
Travenol Laboratories, Inc.	Dr. Aaron M. Josephson (Task Group Member)

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APPENDIX B

PROJECT AREA DISTRIBUTION ANALYSIS



APPENDIX B
PROJECT AREA DISTRIBUTION ANALYSIS

This appendix presents two categories of data displays resulting from analysis of project areas identified by each task group:

- The percentage distribution of project areas with respect to the 10 legislative requirements and
- The percentage distribution of project areas with respect to the four program objectives.

These results were obtained by a subjective comparison of each project area against the legislation requirements and objectives. These distributions do not reflect the relative manpower or funding required in any objective or legislative category since they are based only on the number of project areas identified.



1. Distribution of Project Areas with Respect to the Legislation

Table B-1 presents, on a task group basis, the percentage of project areas which relate to specific legislative planning requirements. The percentage distribution for all the task groups as a composite is shown in Figure B-1; Figure B-2 presents the percentage distribution for each task group. The 10 legislative requirements are as follows:

"... (1) investigation into the epidemiology, etiology, and prevention of all forms and aspects of heart, blood vessel, lung, and blood diseases, including investigations into the social, environmental, behavioral, nutritional, biological, and genetic determinants and influences involved in the epidemiology, etiology, and prevention of such diseases;

"(2) studies and research into the basic biological processes and mechanisms involved in the underlying normal and abnormal heart, blood vessel, lung, and blood phenomena;

"(3) research into the development, trial and evaluation of techniques, drugs, and devices (including computers) used in, and approaches to, the diagnosis, treatment (including emergency medical service), and prevention of heart, blood vessel, lung, and blood diseases and the rehabilitation of patients suffering from such diseases;

"(4) establishment of programs that will focus and apply scientific and technological efforts involving biological, physical, and engineering sciences to all facets of heart, blood vessel, lung, and blood diseases with emphasis on refinement, development, and evaluation of technological devices that will assist, replace, or monitor vital organs and improve instrumentation for detection, diagnosis, and treatment of those diseases;



"(5) establishment of programs for the conduct and direction of field studies, large-scale testing and evaluation, and demonstration of preventive, diagnostic, therapeutic, and rehabilitative approaches to, and emergency medical services for such diseases;

"(6) studies and research into blood diseases and blood, and into the use of blood for clinical purposes and all aspects of the management of its resources in this country, including the collection, preservation, fractionalization, and distribution of it and its products;

"(7) the education and training of scientists, clinicians, and educators in fields and specialties (including computer sciences) requisite to the conduct of programs respecting heart, blood vessel, lung, and blood diseases;

"(8) public and professional education relating to all aspects of such diseases and the use of blood and blood products and the management of blood resources;

"(9) establishment of programs for study and research into heart, blood vessel, lung, and blood diseases of children (including cystic fibrosis, hyaline membrane, and hemolytic and hemophilic diseases) and for the development and demonstration of diagnostic, treatment, and preventive approaches to these diseases; and

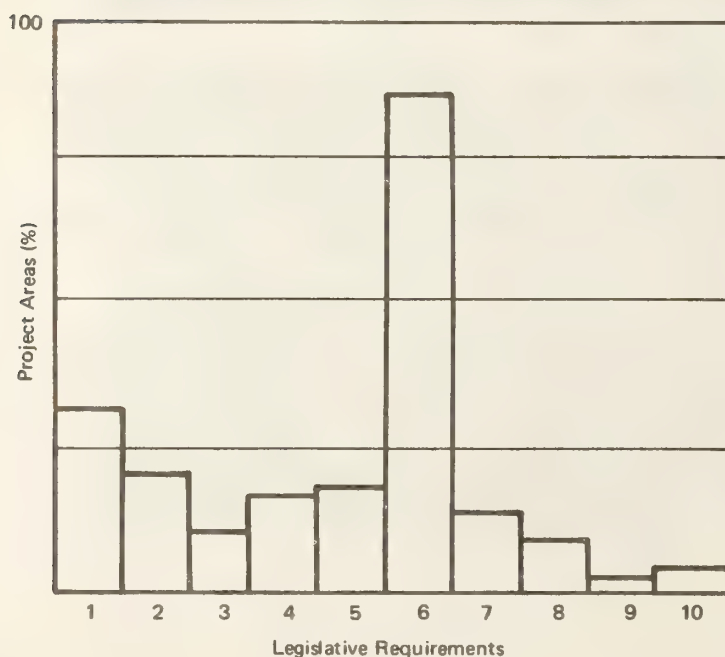
"(10) establishment of programs for study, research, development, demonstrations and evaluation of emergency medical services for people who become critically ill in connection with heart, blood vessel, lung, or blood diseases, which programs shall include programs for (A) the training of paraprofessionals in (i) emergency treatment procedures, and (ii) utilization and operation of emergency medical equipment, (B) the development and operation of (i) mobile critical care units (including helicopters and other airborne units where appropriate), (ii) radio, telecommunications, and other means of communications, and (iii) electronic monitoring systems, and (C) the coordination with other community services and agencies in the joint use of all forms of emergency vehicles, communications systems, and other appropriate services..."



Table B-1
DISTRIBUTION OF PROJECT AREAS WITH RESPECT
TO THE LEGISLATIVE REQUIREMENTS

Task Group	No. of Project Areas	Legislative Requirement									
		1	2	3	4	5	6	7	8	9	10
Collection	27	11%	7%	15%	4%	26%	96%	7%	7%	0	0
Fractionation and Preservation	19	0	16%	0	32%	16%	100%	5%	5%	10%	5%
Laboratory Procedures and Controls	12	50%	0	0	8%	25%	100%	8%	0	0	0
Utilization	29	35%	28%	17%	31%	21%	100%	7%	0	0	0
Systems Management	40	5%	8%	10%	18%	20%	100%	48%	13%	0	8%
Transplantation	48	79%	77%	23%	15%	8%	2%	4%	15%	0	0
TOTAL	175	30%	22%	11%	18%	19%	83%	13%	7%	1%	2%

Figure B-1
COMPOSITE FOR ALL TASK GROUPS

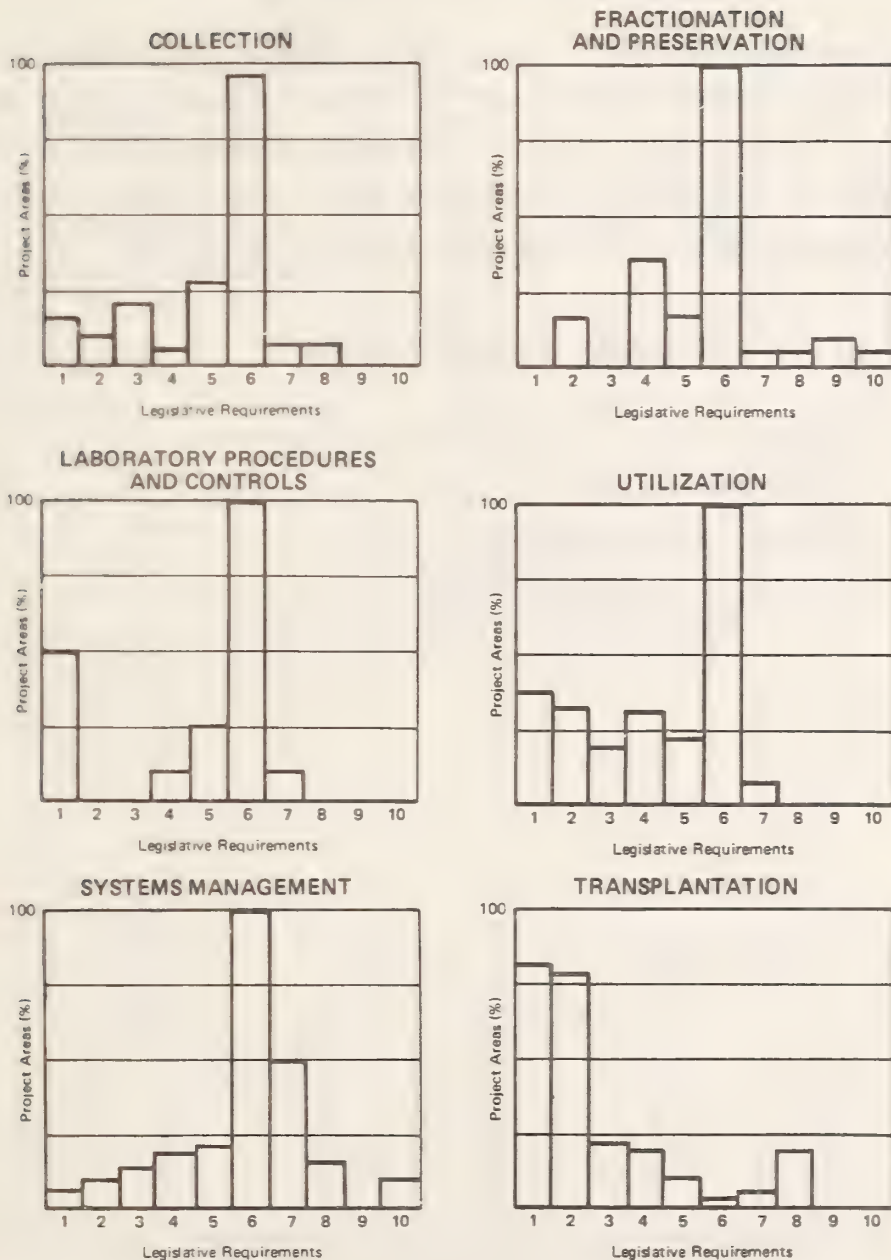


KEY:

- 1 — Epidemiology, Etiology
- 2 — Biological Processes
- 3 — Techniques, Drugs, Devices
- 4 — Bioengineering
- 5 — Field/Clinical Studies
- 6 — Blood Resources
- 7 — Specialist Education
- 8 — Public Education
- 9 — Childhood Diseases
- 10 — Emergency Services



Figure B-2
INDIVIDUAL TASK GROUPS



KEY:

- 1 — Epidemiology, Etiology
- 2 — Biological Processes
- 3 — Techniques, Drugs, Devices
- 4 — Bioengineering
- 5 — Field/Clinical Studies
- 6 — Blood Resources
- 7 — Specialist Education
- 8 — Public Education
- 9 — Childhood Diseases
- 10 — Emergency Services



2. Distribution of Project Areas with Respect to the Program Objectives

Table B-2 presents, on a task group basis, the percentage of project areas which relate to the four primary program objectives. The percentage distribution for all the task groups as a composite is shown in Figure B-3, and Figure B-4 presents the percentage distribution for each task group.

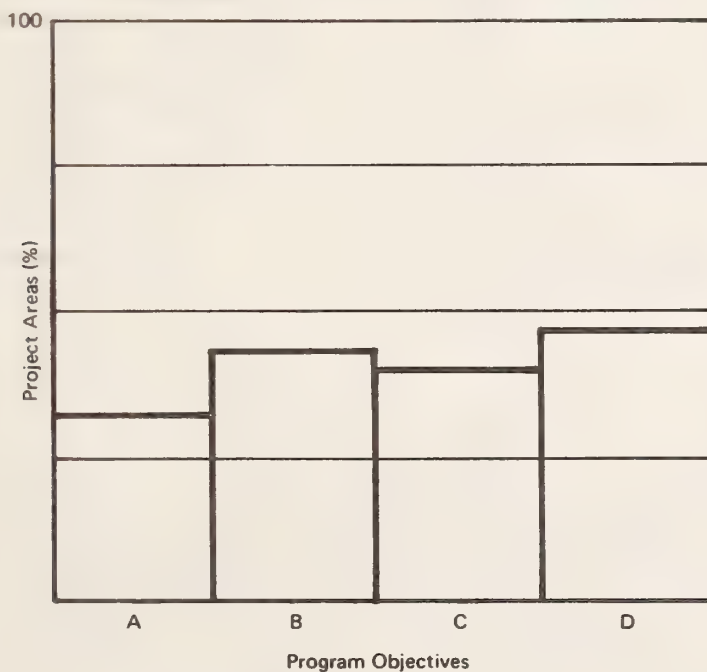
The four primary program objectives are:

- A. Supply
- B. Quality
- C. Systems Effectiveness
- D. Clinical Effectiveness.

Table B-2
DISTRIBUTION OF PROJECT AREAS WITH RESPECT
TO THE PROGRAM OBJECTIVES

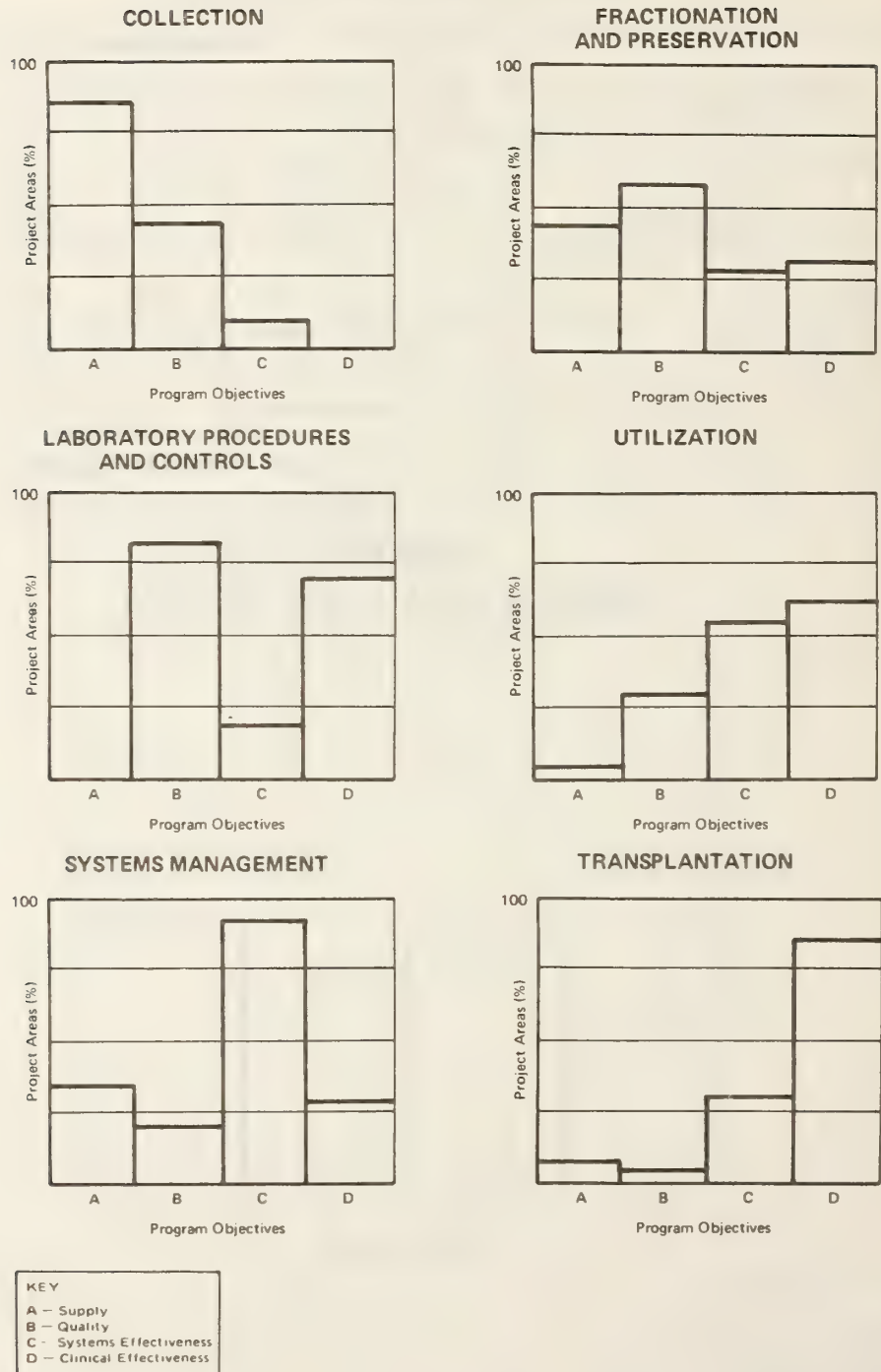
Task Group	No. of Project Areas	Primary Program Objectives			
		A	B	C	D
Collection	27	85%	48%	11%	0
Fractionation and Preservation	19	47%	63%	26%	32%
Laboratory Procedures and Controls	12	0	83%	17%	67%
Utilization	29	3%	28%	55%	62%
Systems Management	40	35%	18%	90%	28%
Transplantation	48	8%	4%	29%	81%
TOTAL	175	30%	41%	38%	45%

Figure B-3
COMPOSITE FOR ALL TASK GROUPS



KEY:
A — Supply
B — Quality
C — Systems Effectiveness
D — Clinical Effectiveness

Figure B-4
INDIVIDUAL TASK GROUPS



APPENDIX C

DATA SUMMARY



APPENDIX C
DATA SUMMARY

This appendix provides a summary of the data base, i.e., the problems, approaches and project areas, which resulted from extensive deliberations of the six Task Groups. A detailed discussion of each of these items is given in the individual Task Group materials.

The number of problems, approaches, and project areas identified by each Task Group are summarized in Table C-1. The listing which follows provides the corresponding titles for each category, ordered by number. The first digit identifies the problem, the second digit the approach, and the third digit the project area.



Table C-1
DATA SUMMARY FOR BLOOD RESOURCES PANEL

No.	Task Group	Problems	Approaches	Project Areas
1	Collection	2	5	27
2	Fractionation & Preservation	2	4	19
3	Laboratory Procedures and Controls	2	3	12
4	Utilization	2	8	29
5	Systems Management	3	7	40
6	Transplantation	3	10	48
TOTAL		14	37	175

DATA SUMMARY FOR
TASK GROUP 1

BLOOD COLLECTION



PROBLEM 1. DONOR RECRUITMENT

- 1.1 Evaluate the Present Donor Recruiting System.
 - 1.1.1 Development of methods to evaluate the techniques used in recruiting.
 - 1.1.2 Characteristics of the donor and nondonor.
 - 1.1.3 Evaluation of attitudes about blood.
 - 1.1.4 Survey of existing collecting systems.
 - 1.1.5 Measurement of incentive effectiveness.
 - 1.1.6 Study human donor motivation.
 - 1.1.7 Cost effectiveness of different methods of recruitment (Ref. Task Group 5 Report).
 - 1.1.8 Effect of recruitment strategies on systems effectiveness (Ref. Task Group 5 Report).
- 1.2 The Safety of the Donor.
 - 1.2.1 Define the extent and nature of physiologic and potential pathologic effects of repeated donation.
 - 1.2.2 The nature and extent of the response to a single donation of a blood component.
 - 1.2.3 Donor care.
- 1.3 Improve Recruitment of High Quality Donors.
 - 1.3.1 Establishment of a national commission and regional forums for procurement.
 - 1.3.2 Development of programs to improve capability of present recruitment personnel.
 - 1.3.3 Hepatitis reporting.
 - 1.3.4 Special donor screening programs (Ref. Task Group 3 Report).
 - 1.3.5 Screening for absence of Iga (Ref. Task Group 3 Report).

PROBLEM 2. BLOOD COLLECTION

- 2.1 Physical Conditions for Blood Component Collection.
 - 2.1.1 Optimum physical conditions for collection of the cellular components of blood.
 - 2.1.2 Optimum physical conditions for the collection of plasma components of blood.
 - 2.1.3 Self-contained mobile vehicle collection centers.
 - 2.1.4 Mobile plasmapheresis (Ref. Task Group 3 Report).
 - 2.1.5 Leukocyte harvesting (Ref. Task Group 3 Report).
 - 2.1.6 Collection of plasma for fractionation (Ref. Task Group 5 Report).
- 2.2 New Instrumentation for Collection and Separation of Blood.
 - 2.2.1 Biomechanical equipment for separation of blood components during collection.
 - 2.2.2 Biomechanical equipment for whole blood collection.
 - 2.2.3 Standards for materials used in blood collection equipment.
 - 2.2.4 Testing for the toxic effects of materials and surfaces.
 - 2.2.5 Devices for sterile connection of collection equipment.

DATA SUMMARY FOR
TASK GROUP 2

FRACTIONATION AND PRESERVATION



PROBLEM 1. COST EFFECTIVENESS

- 1.1 Development and Evaluation of New Blood Products.
 - 1.1.1 Clinical evaluation of refined plasma derivatives.
 - 1.1.2 Variability of plasma components in normal and pathological states.
 - 1.1.3 Synthetic hemostatic agents.
 - 1.1.4 Volume expanders.
 - 1.1.5 Synthetic oxygen transporters.
 - 1.1.6 Platelet transfusion (Ref. Task Group 3 Report).
- 1.2 Cost Relationships of Fractionization and Preservation.
 - 1.2.1 Cost relationships in fractionation.
 - 1.2.2 Effect of methodological changes in cost relationships in fractionation.
 - 1.2.3 Cost relationships in cell preservation.
 - 1.2.4 Effect of methodological changes in cost relationships in erythrocyte preservation.

PROBLEM 2. QUALITY CONTROL OF BLOOD COMPONENTS

- 2.1 Standards and Procedures for Quality Control.
 - 2.1.1 Development of standards to test for safety and efficacy of plasma and cellular products of blood.
 - 2.1.2 Development of flexible, uniform and realistic regulations.
- 2.2 Optimization of Support for Blood Components.
 - 2.2.1 Optimal support for the red blood cells in the liquid state.
 - 2.2.2 Optimal support for frozen red blood cells and their clinical use.
 - 2.2.3 Preservation of platelets in liquid state.
 - 2.2.4 Long-term (frozen) platelet preservation.
 - 2.2.5 Lymphocyte preservation and storage.
 - 2.2.6 Optimal support for granulocyte preservation.
 - 2.2.7 Optimal support during plasma fractionation.



DATA SUMMARY FOR
TASK GROUP 3

LABORATORY PROCEDURES AND CONTROLS



PROBLEM 1. BLOOD PRODUCTS

- 1.1 Quality of Blood Products.
 - 1.1.1 Improvement of regulation of blood products.
 - 1.1.2 Automation of serologic and compatibility testing.
 - 1.1.3 Quality control.

PROBLEM 2. DISEASE TRANSMISSION

- 2.1 Detection and Removal of Disease-Causing Agents.
 - 2.1.1 Development of techniques for the removal or neutralization of disease-causing agents.
 - 2.1.2 Development of test systems for the identification of disease-causing agents in blood, blood components, and blood products.
 - 2.1.3 Development of test models for determining presence and infectivity of disease-causing agents.
 - 2.1.4 Is factor IX concentrate safe for Rx of liver disease?
 - 2.1.5 Studies on the transmission of disease by whole blood and its components (Ref. Task Group 4 Report).
- 2.2 Improve Processing Techniques.
 - 2.2.1 Hepatitis testing.
 - 2.2.2 Reduction of incidence of hepatitis and cytomegalovirus.
 - 2.2.3 Sterile joining.
 - 2.2.4 Quality of pilot tube (Ref. Task Group 4 Report).

DATA SUMMARY FOR
TASK GROUP 4

UTILIZATION



PROBLEM 1. COMPLICATIONS OF TRANSFUSION

- 1.1 The Incidence of Sensitization.
 - 1.1.1 Studies on the sensitization to coagulant factors.
 - 1.1.2 Studies on the incidence of sensitization to plasma proteins.
 - 1.1.3 Studies on the incidence and significance of sensitization to platelets and white cells.
- 1.2 Develop Systematized Blood and Tissue Typing.
 - 1.2.1 Fail-safe identification system.
 - 1.2.2 Complete blood typing.
 - 1.2.3 Tissue typing.
 - 1.2.4 Instrumentation for blood typing.
 - 1.2.5 Automation and EDP (electronic data processing).
- 1.3 Untoward Reactions from Transfusions.
 - 1.3.1 Massive transfusion—its hazards and management.
 - 1.3.2 Studies of untoward reactions to transfusion of whole blood and components.
- 1.4 Techniques for Compatibility Testing.
 - 1.4.1 Compatibility testing.
 - 1.4.2 Prevention of hepatitis B.
 - 1.4.3 Platelet compatibility.
 - 1.4.4 Tests for cytomegalovirus and hepatitis A.

PROBLEM 2. THE TRANSFUSED PRODUCT

- 2.1 Evaluation of Blood Product Use.
 - 2.1.1 Transfusion requirements of the severely burned patient, the neonate, and other unique patient groups.
 - 2.1.2 Compatibility of intravenous solutions with blood and blood products.
 - 2.1.3 Development of animal research models for evaluation of effectiveness of blood and blood products.
- 2.2 Utilization of Blood Products.
 - 2.2.1 Optimal utilization of blood products for management of hemophilia A and B.
 - 2.2.2 Enhancement of effectiveness of transfused leukocyte concentrates and buffy coat-poor red blood cells.
 - 2.2.3 Improvement of availability of transfusion products in the transfusion facility.
 - 2.2.4 Utilization of fractionated albumin (Ref. Task Group 5 Report).
- 2.3 Methods for Delivery of Blood or Tissue.
 - 2.3.1 Frozen blood.
 - 2.3.2 Packaging and facilitation of transfusion.
 - 2.3.3 Organization of delivery services.
 - 2.3.4 Auto transfusion (instant retransfusion).



- 2.3.5 Cost effectiveness of delivery systems (Ref. Task Group 5 Report).
- 2.4 Improve Procedures for Blood Therapy.
 - 2.4.1 Preparation of guidance manuals of blood therapy for clinical use.
 - 2.4.2 Development of transfusion teams.
 - 2.4.3 Utilization and economy of nonspecific transfusions (Ref. Task Group 5 Report).

DATA SUMMARY FOR
TASK GROUP 5

SYSTEMS MANAGEMENT



PROBLEM 1. SYSTEM EFFECTIVENESS

- 1.1 Evaluate the Effectiveness of the Present Blood Banking System.
 - 1.1.1 Evaluation of the blood service systems efficiency.
 - 1.1.2 Blood assurance and insurance programs.
 - 1.1.3 Evaluation of blood and credit exchange systems.
 - 1.1.4 Survey of blood bank technical personnel.
 - 1.1.5 Survey of hospital transfusion facilities.
- 1.2 Standardization of Procedures in Blood Banking.
 - 1.2.1 A lexicon for blood banking.
 - 1.2.2 An operations manual for blood banks.
 - 1.2.3 Blood bank cost and fiscal accounting.
 - 1.2.4 Uniform accounting.
 - 1.2.5 Uniform blood bank records (Ref. Task Group 3 Report).
 - 1.2.6 Blood service inventory systems.
- 1.3 Impact of External Factors and Internal Changes on the System.
 - 1.3.1 The development and introduction of new products and procedure in blood banking.
 - 1.3.2 Impact of new techniques.
 - 1.3.3 Impact of medical practice on supply of blood services.
 - 1.3.4 Transportation problems affecting the efficiency of blood services.
 - 1.3.5 Impact of morbidity and disasters on blood banking.
- 1.4 Reduce Wastage of Blood.
 - 1.4.1 Reduction of in-hospital outdated.
 - 1.4.2 Effect of blood redistribution on outdated.
 - 1.4.3 Rejuvenation of stored blood components (Ref. Task Group 4 Report).
 - 1.4.4 Plasma salvage (Ref. Task Group 4 Report).

PROBLEM 2. COMPREHENSIVE CENTERS

- 2.1 Centers for Research, Development, and Clinical Utilization of Blood, Tissue and Organs.
 - 2.1.1 Development of comprehensive centers dealing with all aspects of research, development, and utilization of blood products (Ref. Task Group 2 Report).
 - 2.1.2 National blood inventory system.
 - 2.1.3 Establishment of a national center for data.
 - 2.1.4 Clinical transplantation research centers (Ref. Task Group 6 Report).
 - 2.1.5 Animal research center (Ref. Task Group 4 Report).
 - 2.1.6 Planning and development for regional centers.
 - 2.1.7 Development of a scientific base.

PROBLEM 3. PROFESSIONAL STANDARDS

- 3.1 Education and Training of Specialists.
 - 3.1.1 Standards and qualifications for blood banking directors (Ref. Task Group 4 Report).
 - 3.1.2 Training programs for blood bank medical directors.
 - 3.1.3 Education of physician specialists in the requirements of transfusion service (Ref. Task Group 4 Report).
 - 3.1.4 Training hospital administrative staff (Ref. Task Group 4 Report).
 - 3.1.5 Professional management for blood banks (Ref. Task Group 4 Report).
 - 3.1.6 Training of M.D. clinical transfusionists (Ref. Task Group 4 Report).
 - 3.1.7 Surgical immunologists (Ref. Task Group 6 Report).
 - 3.1.8 Training of tissue procurement technicians (Ref. Task Group 6 Report).
 - 3.1.9 Blood processing technician training (Ref. Task Group 3 Report).
- 3.2 Training of Scientists in Blood Processing.
 - 3.2.1 Development of mechanisms for improving recruitment, training, and retention of career scientists in blood processing (Ref. Task Group 2 Report).
 - 3.2.2 Evaluation of strengths and weaknesses of existing educational and training programs (Ref. Task Group 2 Report).
 - 3.2.3 Development of methods to retrain and update present personnel (Ref. Task Group 2 Report).
 - 3.2.4 Program expansion in continuing education in blood processing and technology (Ref. Task Group 3 Report).

PROBLEM 1. PROCUREMENT AND PRESERVATION OF ORGANS AND TISSUES

- 1.1 Evaluate the Effect of Storage on Tissue, Organs and Blood Components.
 - 1.1.1 Modification of antigens in stored tissues and organs.
 - 1.1.2 Clinical evaluation of organ preservation.
 - 1.1.3 Guidelines for organ preservation.
 - 1.1.4 Long-term preservation of organs.
 - 1.1.5 Short-term organ preservation.
 - 1.1.6 Preservation of platelets and white cells.
- 1.2 Improve Procedures for Procurement of Blood, Bone Marrow, Tissue and Organs.
 - 1.2.1 Walking donor bank for blood components and bone marrow.
 - 1.2.2 Organ procurement and distribution.
 - 1.2.3 Regional all-inclusive tissue procurement facilities.
 - 1.2.4 Medico-legal support.
- 1.3 Promote Understanding of Transplantation.
 - 1.3.1 Legal definition of brain death.
 - 1.3.2 Medical and lay education regarding transplantation.

PROBLEM 2. IMMUNOLOGICAL AND GENETIC ASPECTS OF TRANSPLANTATION

- 2.1 Improve Understanding of Human Transplantation Antigens.
 - 2.1.1 Development and evaluation of reliable tests to detect presensitization to transplantation antigens.
 - 2.1.2 Identification of non-HL-A transplantation antigens.
 - 2.1.3 HL-A as transplantation antigens.
 - 2.1.4 Detection and definition of the full spectrum of HL-A antigens.
 - 2.1.5 Use of purified transplantation antigens as tolerogens.
 - 2.1.6 Organ transplants perfectly matched for HL-A.
 - 2.1.7 Removal of transplant antigens from blood.
- 2.2 Study the Immune Response Genes in Man.
 - 2.2.1 To develop in vitro and in vivo tests of immune response genes in man.
 - 2.2.2 To study the immune response genes in relation to HL-A.
 - 2.2.3 Tests of the vigor of the rejection response.
 - 2.2.4 Development of improved methods of nonspecific immune suppression.
 - 2.2.5 Develop specific alterations of the immune response.
 - 2.2.6 Nature of the enhancing factor.
 - 2.2.7 Selection of effective regimens for enhancement.
- 2.3 Study Techniques for Improving Graft Survival.
 - 2.3.1 Predictive value of mixed lymphocyte culture (MLC).
 - 2.3.2 Continuing evaluation of the predictive value of tissue typing and transplant survival.

- 2.3.3 Effect of prior in vitro residence on allograft survival.
- 2.3.4 Cellular and humoral responses in allograft recipients.
- 2.3.5 Immune suppression by liver grafts in pigs.

PROBLEM 3. PATIENT MANAGEMENT

- 3.1 Study and Develop Methods of Typing and Histocompatibility.
 - 3.1.1 Development of monospecific serological typing reagents.
 - 3.1.2 Family studies of histocompatibility in immunogenetics.
 - 3.1.3 Determination of the relative immunogeneity of various HL-A specificities.
 - 3.1.4 New methods of detection of histocompatibility markers in vitro.
- 3.2 Study Preimmunization and Presensitization.
 - 3.2.1 Role of non-HL-A antibodies in crossmatching.
 - 3.2.2 Crossmatch tests for cell-mediated responses.
 - 3.2.3 Identification of plasma factors which block in vitro measures of cell-mediated immunity.
 - 3.2.4 Influence of previous exposure to microorganisms.
 - 3.2.5 Methods of avoiding presensitization.
 - 3.2.6 Elimination of presensitization.
- 3.3 Diagnosis, Prevention, and Treatment of Infections.
 - 3.3.1 Study of platelets and granulocytes.
 - 3.3.2 Environmental control of infection in immunosuppressed patients.
 - 3.3.3 Prevention of serious infections.
 - 3.3.4 Diagnosis and treatment of viral, fungal and parasitic infections.
- 3.4 Understanding the Human Factors of Patients Having Transplants.
 - 3.4.1 Quality of life following kidney transplant.
 - 3.4.2 Transplantation expenses.
 - 3.4.3 Human factors—pre- and posttransplant

DATA SUMMARY FOR
TASK GROUP 6

TRANSPLANTATION



U.S. DEPARTMENT OF HEALTH, EDUCATION AND WELFARE
Public Health Service
National Institutes of Health
National Heart and Lung Institute
DHEW Publication No. (NIH) 73-521



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